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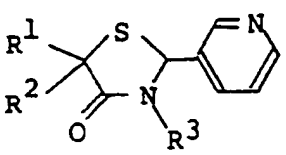
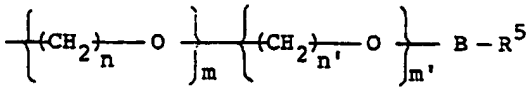
(54) Novel thiazolidin-4-one derivatives and acid addition salts thereof.

(57) Thiazolidin-4-one derivatives are represented by the following general formula (I)



(I)

wherein:
R^1 and R^2 are the same or different and denote each
(i) a residue represented by the general formula
-A-R^4
wherein, A denotes a single bond, C_1-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene and R^4 denotes hydrogen, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl, or C_1-C_6 haloalkyl, or
(ii) a residue represented by the general formula



wherein, B denotes a single bond or C_1-C_6 alkylene, R^5 denotes hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl, substituted silyl, or substituted or unsubstituted

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aryl, n and n' denote each an integer of 2 to 4, m denotes an integer of 1 to 3, and m' denotes an integer of 0 to 2; and R^3 denotes hydrogen, C_1-C_2 alkyl, allyl, 2-propynyl, or a residue represented by

(a) the general formula

$$-\!\!\left(CH_2\right)_{\ell}\!\!- R^6$$

wherein, R^6 denotes halogen, an aryl group substituted or unsubstituted by one or more hydroxy or C_1-C_4 alkoxy groups, or a residue represented by the general formula -D-R^7 (D denotes oxygen or sulfur and R^7 denotes hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkanol) and ℓ denotes an integer of 2 to 4,

(b) the general formula

$$-\!\!\left(CH_2\right)_{k}\!\!- CO - E - R^8$$

wherein, E denotes oxygen, sulfur, imino, or C_1-C_4 alkylimino, R^8 denotes hydrogen or C_1-C_4 alkyl, or -(E-R^8) denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms, and k denotes an integer of 1 to 3, or

(c) the general formula

-F-R^9

wherein, F denotes C_2-C_6 alkylene and R^9 denotes a nitrogen-containing heterocyclic aromatic residue or an amino group represented by the general formula

$$-N\begin{matrix} R^{11} \\ \diagup \\ \diagdown \\ R^{10} \end{matrix}$$

(R^{10} denotes hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkyl or R^{10} in combination with R^{11} denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms), with the proviso that, when R^1 is hydrogen and R^2 is methyl, R^3 denotes hydrogen, C_1-C_2 alkyl, 2-propynyl, or a residue represented by

(a) the general formula

$$-\!\!\left(CH_2\right)_{\ell}\!\!- R^6$$

wherein, R^6 denotes halogen, an aryl group substituted or unsubstituted by one or more hydroxy or C_1-C_4 alkoxy groups, or a residue represented by the general formula -D-R^7 (D denotes oxygen or sulfur and R^7 denotes hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkanoyl) and ℓ denotes an integer of 2 to 4,

(b) the general formula

$$-\!\!\left(CH_2\right)_{k}\!\!- CO - E - R^8$$

wherein, E denotes oxygen, sulfur, imino, or C_1-C_4 alkylimino, denotes hydrogen or C_1-C_4 alkyl, or -(E-R^8) denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms, and k denotes an integer of 1 to 3, or

(c) the general formula

-F-R^9

wherein, F denotes C_2-C_6 alkylene and R^9 denotes a nitrogen-containing heterocyclic aromatic residue or an amino group represented by the general formula

$$-N\begin{matrix} R^{11} \\ \diagup \\ \diagdown \\ R^{10} \end{matrix}$$

(R^{10} denotes hydrogen, C_2-C_4 alkyl or C_1-C_4 alkanoyl and R^{11} denotes hydrogen or C_1-C_4 alkyl or R^{10} in combination with R^{11} denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms.

Since these derivatives, and acid addition salts thereof have selective PAF-antagonistic activities, these compounds are very useful as preventive and curative agents for PAF-induced diseases, for example, various kinds of inflamation, allergic diseases, circulatory diseases, and gastro-intestinal diseases.

Descripti n

NOVEL THIAZOLOIDIN-4-ONE DERIVATIVES AND ACID ADDITION SALTS THEREOF

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to novel 2-pyridyl-tiazolidin-4-one derivatives which shown excellent antagonisms to the platelet activating factor (hereinafter abbreviated as PAF).

DESCRIPTION OF THE PRIOR ART

PAF is a factor which in minute amounts can activate rabbit blood platelets. This factor was found in the supernatant of a culture of antigen-stimulated basophils of IgE-sensitized rabbits [Benveniate, J. et al J.P. Med., 136, 1356-1377 (1972)]. PAF is an autocoid present in living bodies which has been identified as acetyl glyceryl ether phosphorylcholine (AGEPC), i.e. 1-O-hexadecyl/octadecyl-2-o-acetyl-sn-glyceryl-3-phosphorylcholine [Hanahan, D.J. et al., J. Biol. Chem, 254, 9355-9385 (1979)].

It is known that in addition to the platelet activation, PAF in extremely low concentrations exhibits various physiological actions, e.g. the depression of blood pressure, increase in vascular permeability, contraction of smooth muscle, activations of leucocyte-, monocyte, and macrophage, and acceleration of liver glycogen decomposition.

These physiological actions are regarded as being associated with a number of diseases, e.g. various kinds of inflammation, allergic diseases, circulatory diseases, and gastrointestinal diseases. Accordingly, the search of PAF-antagonists has been focused and energetically conducted in recent years for the purpose of preventing and/or treating these PAF-induced diseases.

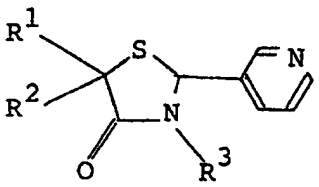
However, while several compounds have been tested up to now to treat or prevent PAF-induced diseases, their effectiveness are not fully satisfactory.

On the other hand, a great number of studies are reported which relate to thiagolidin-4-one derivatives. Of these studies, however, those relating to 2-pyridylthiazolidin-4-one derivatives are reported only by the following seven documents: Japanese Patent Application Kokai (Laid-Open) No. 145670/79 discloses N-(substituted or unsubstituted phenyl and pyridyl) derivatives of 2-pyridylthiazolidin-4-one which are useful as agricultural chemicals. Japanese Patent Application Kokai No. 55184/80 discloses compounds including chiefly N-(substituted or unsubstituted phenyl, benzyl, and cycloalkyl) derivatives of 2-pyridylthiazolidin-4-one which are useful as agricultural chemicals. Japanese Patent Application Kokai Nos. 85380/82 and 88170/82 disclose the N-carboxycyclohexylmethyl derivatives of 2-pyridylthazolidin-4-one and the N-carboxymethylphenyl derivatives of the same compounds respectively, the former having an anti-complementary activity and the latter having antiinflammatory, analgesic, and antirheumatic activities. Japanese Patent Application Kokai No. 183689/83 discloses the N-pyrazinyl derivative of 2-pyridylthiazolidin-4-one useful as an agricultural chemical. U.S. Patent No. 4,501,746 discloses N-(substituted phenyl) derivatives of 2-pyridylthiazolidin-4-one which are useful as intermediates in syntheses. Further, Japanese Patent Application Kokai No. 103881/86 discloses N-(substituted carbamoyloxy) derivatives of 2-pyridylthazolidin-4-one which are useful as cardiotonica.

SUMMARY OF THE INVENTION

Under such circumstances as stated above, the present inventors made intensive studies with the object of searching out a useful PAF-antagonistic agent. As a result, it has been found that thiazolidin-4-one derivatives represented by the following general formula [I] and acid addition salts thereof have selective PAF-anatagonistic activities and are very useful therapeutic agents for preventing and/or treating PAF-induced diseases, for example, various kinds of inflammation, allergic diseases, circulatory diseases, and gastrointestinal diseases.

General formula [I]



wherein;

R^1 and R^2 are the same or different and denote each

(I) a residue represented by the general formula

-A-R^4

wherein, A denotes a single bond, C_1-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene and R^4 denotes hydrogen, C_1-C_{12} alkyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, or C_1-C_6 haloalkyl, or

(ii) a residue represented by the general formula

$$-\{-(CH_2)_n-O\}_m-\{-(CH_2)_{n'}-O\}_{m'}-B-R^5$$

wherein, B denotes a single bond or C_1-C_6 alkylene, R^5 denotes hydrogen, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl, substituted silyl, or substituted or unsubstituted aryl, n and n' denote each an integer of 2 to 4, m denotes an integer of 1 to 3, and m' denotes an integer of 0 to 2; and R^3 denotes hydrogen, C_1-C_2 alkyl, allyl, 2-propynyl, or a residue represented by

(a) the general formula

$$-\{-CH_2\}_\ell R^6$$

wherein, R^6 denotes halogen, an aryl group substituted or unsustituted by one or more hydroxy or C_1-C_4 alkoxy groups, or a residue represented by the general formula -D-R^7 (D denotes oxygen or sulfur and R^7 denotes hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkanoyl) and ℓ denotes an integer of 2 to 4,

(b) the general formula

$$-\{-CH_2\}_k-CO-E-R^8$$

wherein, E denotes oxygen, sulfur, imino, or C_1-C_4 alkylimino, R^8 denotes hydrogen or C_1-C_4 alkyl, or -(E-R^8) denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms, and k denotes an integer of 1 to 3, or

(c) the general formula

-F-R^9

wherein, F denotes C_2-C_6 alkylene and R^9 denotes a nitrogen-containing heterocyclic aromatic residue or a residue represented by the general formula

$$-N\begin{matrix}R^{11}\\ \diagdown\\ R^{10}\end{matrix}$$

(R^{10} denotes hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkanoyl and R^{11} denotes hydrogen or C_1-C_4 alkyl or R^{10} in combination with R^{11} denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms).

Based on this finding, the present invention has been accomplished.

DETAILED DESCRIPTION OF THE INVENTION

In this specification, the "C_1-C_{12} alkyl" means any of linear and branched alkyl groups including, e.g. methyl, ethyl, n-propyl, n-butyl, sec-butyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, and n-dodecyl; the "C_2-C_8 alkenyl" means any of linear and branched C_2-C_8 alkenyl groups including, e.g. vinyl, 2-propenyl, 2-butenyl, 3-methyl-2-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 2-hexenyl, 4-hexenyl, 5-methyl-4-hexenyl, 2-heptenyl, 6-methyl-5-heptenyl, 2-octenyl, and 6-octenyl; the "C_3-C_8 cycloalkyl" means any of substituted or unsubstituted C_3-C_8 cycloalkyl groups including, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and 1-methyl-cyclohexyl; the "C_1-C_6 haloalkyl" means any of halogenated C_1-C_6 alkyl groups including, e.g. monofluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, nonafluorobutyl, undecafluoropentyl, and tridecafluorohexyl; the "substituted or unsubstituted aryl" means any of substituted or unsubstituted aryl groups including, e.g. phenyl, naphthyl, p-chlorophenyl, o-chlorophenyl, p-fluorophenyl, 2,6-dichlorophenyl, p-methoxyphenyl, and 3,4-dimethoxyphenyl; the "C_1-C_8 alkylene" means any of linear and branched C_1-C_8 alkylene-groups including, e.g. methylene, ethylene, trimethylene, 1-m thyltrimethylene, tetramethylene, pentamethylene, hexamethylene, and heptamethylene; the "C_2-C_8 alkenylene" means any of linear and branched C_2-C_8 alkenyl ne groups including, e.g. vinylene, propenylen , 2-butenbutenylen , 2-m thyl-2-butenylene, 2-pentenylen , 3-pentenylen , 2-hexenyl ne, 3-m thyl-2-hexenylene, 3-heptenylen , and 4-oct nyl ne; the "C_2-C_8 alkynylene" means any of linear and branched C_2-C_8 alkynylene groups including .g. ethynylen , propynyl n , 2-butynylene, 2-methyl-2-butynylene, 2-pentynylene, 3-pentynylene, 2-hexynyl ne, 3-m thyl-2-hexynyl ne,

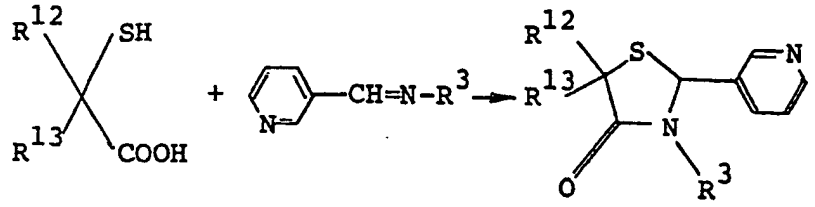
3-heptynylene, and 4-octynyl n ; the "C_1-C_6 alkylene" means any f linear and branched C_1-C_6 alkylene groups including, e.g. m thyl ne, ethylene, trimethylene, 1-methyltrimethylene, tetramethylen , pentamethylene, and hexamethylene; the "C_1-C_6 alkyl" means any of linear and branched C_1-C_6 alkyl groups including, .g. m thyl, ethyl, n-propyl, n-butyl, sec-butyl, n-pentyl, isopentyl, and n-hexyl; the "substituted silyl" means any of groups including, e.g. trimethylsilyl, triethylsilyl, isopropyldimethylsilyl, t-butyldimethylsilyl, methyldiisopropylsilyl, methyldi-t-butylsilyl, tribenzylphenyltriisopr pylsilyl, and triphenylsilyl; the "C_1-C_2 alkyl" means methyl or ethyl; the "halogen" means a halogen atom such as fluorine, chlorine, or bromine; the "C_1-C_4 alkoxy" means any of linear and branched C_1-C_4 alkoxy groups including, e.g. methoxy, ethoxy, n-propoxy, isopropoxy, and n-butoxy; the "C_1-C_4 alkyl" means any of linear and branched C_1-C_4 alkyl groups including, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, and isobutyl; the "C_1-C_4 alkanoyl" means any of linear and branched C_1-C_4 alkanoyl groups including, e.g. formyl, acetyl, propionyl, butyryl, and isobutyryl; the "C_1-C_4 alkylimino" means, e.g. methylimino, ethylimino, n-propylimino, or isobutylimino group; the "5- to 7-membered cyclic amino group" means, e.g. pyrrolidinyl, piperidinyl, homopiperidinyl, morpholinyl, piperazinyl, or N-methylpiperazinyl; the "C_1-C_6 alkylene" means any of linear and branched C_1-C_6 alkylene groups including, e.g. methylene, ethylene, trimethylene, 1-methyltrimethylene, tetramethylene, pentamethylene, and hexamethylene; and the "nitrogen-containing heterocyclic aromatic residue" means e.g. pyrrole, imidazole, or pyrazole ring.

Acid addition salts of thiazolidin-4-one derivatives represented by the general formula [I] are pharmaceutically acceptable salts including; salts with mineral acids, e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid; salts with organic carboxylic acids, e.g. formic acid, acetic acid, fumaric acid, maleic acid, citric acid, lactic acid, malic acid, tartaric acid, and aspartic acid; and salts with sulfonic acids, e.g. methanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, hydroxybenzenesulfonic acid, dihydroxybenzenesulfonic acid, and naphthalenesulfonic acid.

Compounds used in the invention include optical isomer, geometrical isomers, and moreover, hydrates and various crystal forms thereof.

Thiazolidin-4-one derivatives represented by the general formula [I] can be prepared, for example, by the following methods (a) to (k).

(a)



[II] [III] [I]

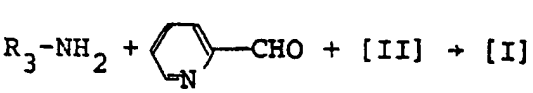
In this equation, R^{12} and R^{13} are the same or different and denote each a residue represented by the general formula

-A-R^4

(wherein A and R^4 are as defined above) and R^3 is as defined above.

That is, the present inventive compound [I] can be prepared by subjecting the thioglycolic acid derivative [II] and the Schiff's base [III] to ring closure in an inert solvent. Such solvents include benzene, toluene, xylene, dichloromethane, 1,2-dichloroethane, chloroform, and tetrahydrofuran, which are commonly used as inert solvents in dehydration reactions, and mixtures of these solvents with ethanol or the like. While this reaction can be carried out at temperatures of 20°C to the reflux temperature, it is preferable with azeotropic dehydration, thereby promoting the reaction.

(b)



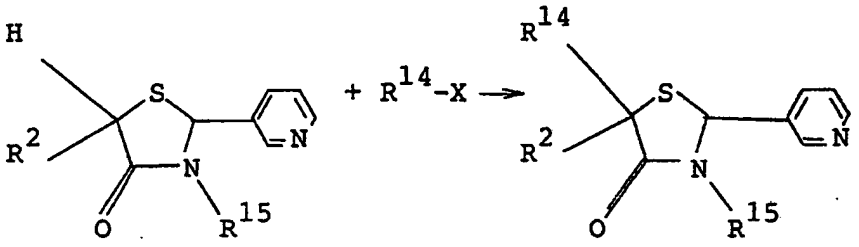
[IV]

In this equation, R^3 is as defined above.

That is, the compound [I] can be prepared by subjecting the primary amine [IV], the compound [II], and nicotin aldehyd to ring closure in an inert solvent. Similarly to the method (a), suitable inert solvents are

benzene, toluene, xylene, dichloromethane, 1,2-dichloroethane, chloroform, tetrahydrofuran, etc. and mixtures of these solvents with ethanol or the like. While this reaction can also be carried out at temperatures of 20°C to the reflux temperature, it is preferable with azeotropic dehydration, thereby promoting the reaction.

(c)

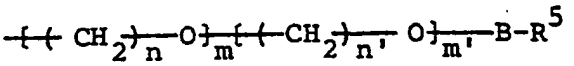


[Ia] [V] [Ib]

In this equation, R^{14} is a residue represented by either the general formula

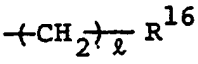
-A-R^4

(wherein A and R^4 are as defined above) or the general formula



(wherein, B, R^5, n, n', m, and m' are as defined above) and

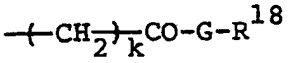
R^{15} denotes C_1-C_6 alkyl, allyl, 2-propynyl, or a residue by (i) the general formula



(wherein, R^{16} denotes an aryl group substituted or unsubstituted by one or more C_1-C_4 alkoxy groups, or a residue represented by the general formula

-D-R^{17}

(wherein, R^{17} denotes C_1-C_4 alkyl and D is as defined above and ℓ is as defined above), (ii) the general formula



(wherein, G denotes oxygen atom or C_1-C_4 alkylimino, R^{18} denotes C_1-C_4 alkyl, or the G-R^{18} combination denotes a 5- to 7-membered heterocyclic amino group which may or may not contain other hetero atoms, and k is as defined above), or (iii) the general formula

-F-R^9

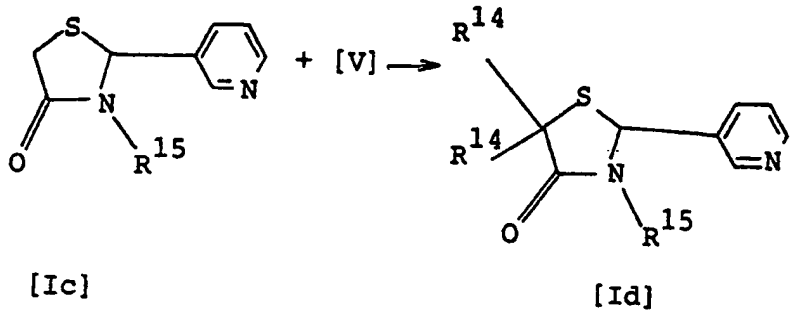
(wherein F and R^9 are as defined above),

X denotes a leaving group and R^2 is as defined above.

The leaving group X can be exemplified by; halogen atoms such as chlorine, bromine, and iodine; lower alkylsulfonyloxy groups such as methylsulfonyloxy and ethylsulfonyloxy; substituted or unsubstituted arylsulfonyloxy groups such as phenylsulfonyloxy and tolylsulfonyloxy; and acyloxy groups such as acetyloxy and benzoyloxy. Of these groups, preferred are halogen atoms, e.g. bromine and iodine.

That is, the compound [Ib] can be prepared by reacting the compound [V] with the compound [Ia] in the presence of a base. Suitable bases for this reaction include; organo-alkali metal compounds, e.g. butyllithium; alkali metal amides, e.g. lithium diisopropylamide; alkali metal hydrides, e.g. sodium hydride; alkali metal alkoxides, e.g. potassium tert-butoxide; and other organic bases, e.g. 1,5-diazabicyclo[4,3,0]nonane-5-ene, 1,8-diazabicyclo[5,4,0]undecane-7-ene, N-methylmorpholine, and 4-dimethylaminopyridine. Desirably, the reaction is conducted in an inert solvent, e.g. tetrahydrofuran, dioxane, n-hexane, or toluene, at a temperature of -50°C to the reflux temperature.

(d)

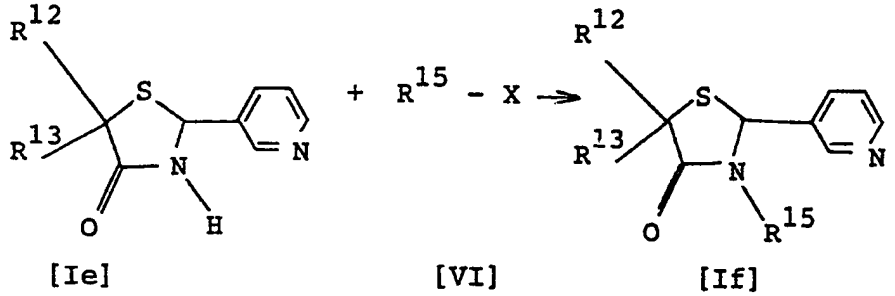


[Ic] [Id]

In this equation, R^{14} and R^{15} are as defined above.

Thus, the compound [Id] can be prepared by reacting the compound [V] with the compound [Ic] in the presence of a base. Suitable bases include; organo alkali metal compounds, e.g. butyllithium; alkali metal amides, e.g. lithium diisopropylamide; alkali metal hydrides, e.g. sodium hydride; alkali metal alkoxides, e.g. potassium tert-butoxide; and other organic bases, e.g. 1,5-diazabicyclo [4.3.0] nonane-5-ene, 1,8-diazabicyclo [5.4.0] undercane-7-ene, N-methylmorpholine, and 4-dimethylaminopyridine. Desirably, the reaction is conducted in an inert solvent, e.g. tetrahydrofuran, dioxane, n-hexane, or toluene, at a temperature of -50°C to the reflux temperature.

(e)

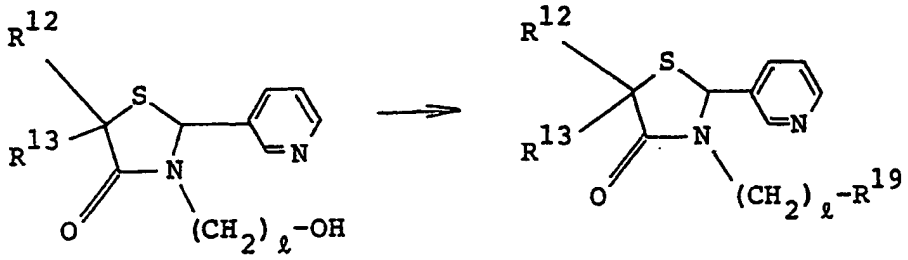


[Ie] [VI] [If]

In this equation, X denotes a leaving group and R^{12}, R^{13}, and R^{15} are as defined above.

Thus, the compound [IF] can be prepared by reacting the compound [VI] with the compound [Ie] in the presence of a base. Suitable bases include; organo alkali metal compounds, e.g. butyllithium; alkali metal amides, e.g. lithium diisopropylamide; alkali metal hydrides, e.g. sodium hydride; alkali metal alkoxides, e.g. potassium tert-butoxide; and other organic bases, e.g. 1.5-diazabicyclo[4.3.0] nonane-5-ene, 1,8-diazabicyclo[5,4,0]undecane-7-ene, N-methylmorpholine, and 4-dimethylaminopyridine. Desirably, the reaction is conducted in an inert solvent, e.g. tetrahydrofuran, dioxane, n-hexane, or toluene under cooling with ice or at room temperature though feasible under heating.

(f)

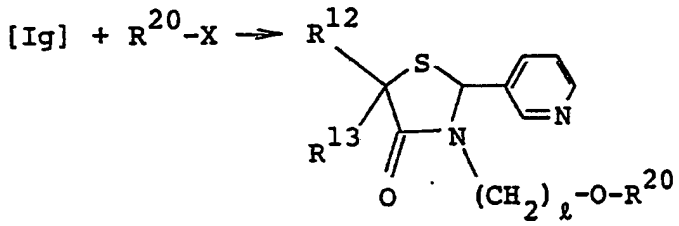


[Ig] [Ih]

In this equation, R^{19} denotes halogen and R^{12}, R^{13}, and ℓ are as defined above.

That is, the compound [Ih] can be prepared by replacing the hydroxy group of compound [Ig] with a halogen atom. This replacement can be achieved by using, for example, phosphorus tribromide, phosphorus pentachloride, or thionyl chloride as a halogenating reagent, preferably in the presence of an organic base such as pyridine. Thus, the compound [Ih] is obtained by carrying out the reaction in a solvent selected from halogenated hydrocarbons such as dichloromethane, chloform, and 1,2-dichloroethane and aromatic hydrocarbons such as benzene and toluene while cooling with ice or heating under reflux. The use of a triphenyl phosphine-carbon tetrachloride mixture is an effective methods of the halogenation.

(g)

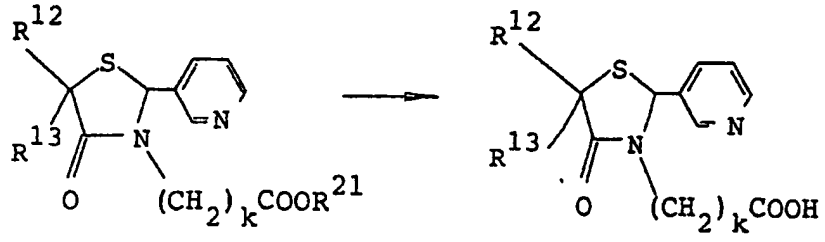


[VII] [Ii]

In this equation, R^{20} denotes C_1-C_4 alkyl or C_1-C_4 alkanoyl, X denotes leaving group, and R^{12}, R^{13} and ℓ are as defined above.

That is, the compound [Ii] can be prepared by reacting the compound [Ig] with the compound [VII], preferably in the presence of a base. When R^{20} is C_1-C_4 alkyl, the reaction is carried out in a solvent such as dimethylformamide, dimethylsulfoxide, or tetrahydrofuran in the presence of an inorganic base such as sodium hydride, potassium hydroxide, or potassium carbonate or an organic base such as pyridine or triethylamine while cooling with ice or heating under reflux. When R^{20} is C_1-C_4 alkanoyl, the reaction is conducted desirably by using an organic base such as pyridine or triethylamine and a solvent selected from aromatic hydrocarbons such as benzene and toluene, ether solvents such as tetrahydrofuran, the above-mentioned organic bases, and alkanoylating reagents, while cooling with ice or heating under reflux.

(h)

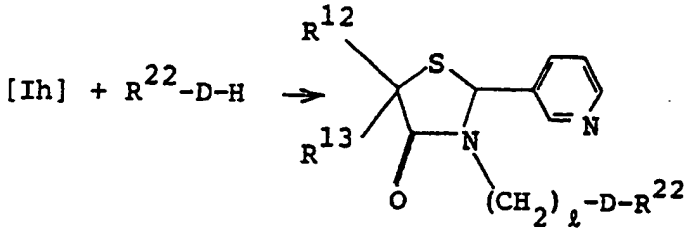


[Ij] [Ik]

In this equation, R^{21} denotes C_1-C_4 alkyl and R^{12}, R^{13} and k are as defined above.

The compound [Ik] can be prepared by hydrolyzing the compound [IJ] in the presence of an acid or base catalyst under conditions of common ester hydrolysis (S. Coffey, "Rodd's Chemistry of Carbon Compounds" 2nd Ed., Vol. 1c, Elsevier (1965), p.92). For instance, the reaction is conducted at room temperature or under heating in the presence of sodium hydroxide or potassium hydroxide by using an alcohol such as methanol or ethanol or water as a solvent.

(i)

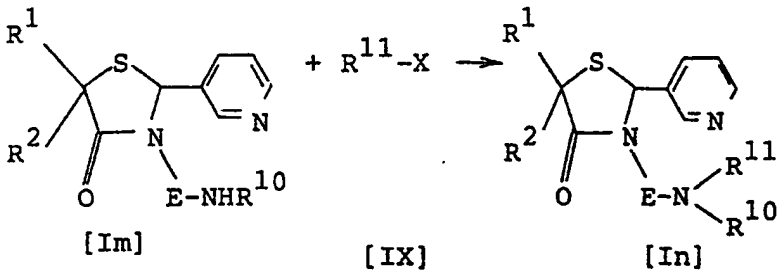


[VIII] [Iℓ]

In this equation, R^{22} denotes C_1-C_4 alkyl or C_1-C_4 alkanoyl and R^{12}, R^{13}, D, and ℓ are as defined above.

The compound [Iℓ] is prepared by reacting the compound [Ih] with the compound [VIII], preferably in the presence of a base. For instance, the reaction is conducted in a solvent selected from aromatic hydrocarbons such as benzene and toluene, halogenated hydrocarbons such as chloroform and dichloroethane, ethers such as tetrahydrofuran, and dimethylformamide and the like in the presence of an inorganic base such as sodium hydroxide, potassium hydroxide, potassium carbonate, or sodium hydrogencarbonate or an organic base such as pyridine or triethyl amine, while cooling with ice or heating under reflux.

(j)



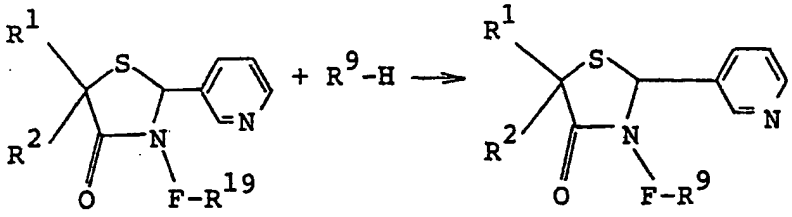
[Im] [IX] [In]

In this equation, X, R^1, R^2, R^{11}, R^{10}, and E are as defined above.

The compound [In] can be prepared by reacting the compound [Im] with the compound [IX] in th presence of a base. Suitable bases include; organic alkali metal compounds, e.g. butyllithium; alkali metal amides, .g. lithium diisopropylamide; and alkali metal hydrides, e.g. sodium hydride. The reaction is conducted in a common organic solvent (e.g. tetrahydrofuran, dioxane, n-hexane, toluene, or dimethylf rmamide) fitt d for

the bas to use, preferably under co ling with ice or at room temperature though the reaction is feasible under heating.

(k)

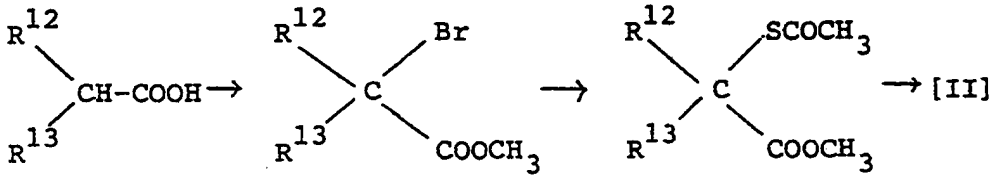


[Ip] [X] [Ig]

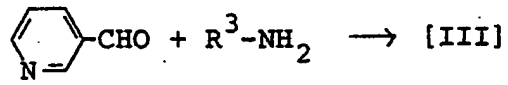
In this equation, R^1, R^2, R^9, R^{19}, and F are as defined above.

The compound [Ig] can be prepared by reacting the compound [Ip] with the compound [X] in the presence of a base. Suitable bases include; organic alkali metal compounds, e.g. butyllithium; alkali metal amides, e.g. lithium diisopropylamide; and alkali metal hydrides, e.g. sodium hydride. The reaction is conducted in a common organic solvent (e.g. tetrahydrofuran, dioxane, n-hexane, toluene, or dimethylformamide) fitted for the base to use, preferably under cooling with ice or at room temperature though the reaction is feasible under heating.

Those raw materials for use in the above reactions are known compounds per se or can be synthesized by known methods. For example, the compounds [II], [III], and [XVII] could be prepared, as shown later in reference examples, in the following ways:



[XI] [XII] [XIII]



[IV]

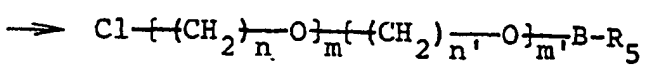
In these equations, R^{12}, R^{13} and R^3 are as defined above.

That is, the starting compound [XI] was esterified and brominated according to the method of E. Schwenk et al. (J. Am. Chem. Soc., 70, 3626 (1948)) to give a compound [XII], which was then converted into a thiol ester derivative [XIII] according to the method described in Shin Jikken Kagaku Koza (A New Course of Experimental Chemistry), Vol. 14, p. 1712. The compound [XIII] was hydrolyzed with a base such as sodium hydroxide or potassium hydroxide in a water-alcohol solvent mixture, thereby preparing the mercaptan derivative [II].

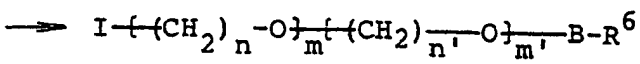
The Schiff's base compound [III] was prepared by subjecting 3-pyridinecarboxyaldehyde and a primary amine [IV] to dehydration-condensation according to the method described in Shin Jikken Kagaku Koza, Vol. 14, page 1410.

The compound [XVII] was prepared by the following route.

[XIV] [XV]



[XVI]



[XVII]

That is, a starting compound [XIV] was converted into a methanesulfonyl derivative [XV] according to the method described in Shin Jikken Kagaku Koza, Vol. 14(III), page 1797. This compound [XV] was converted into a compound [XVI] according to the method of W. T. Olson et al (J. Am. Chem. Soc., 69, 2451 (1947)). Then, the compound [XVII] was derived from the compound [XVI] according to the method described in Shin Jikken Kagaku Koza, Vol. 14(I), page 438.

Starting compounds [Ia], [Ic], [Ie], [Ig], [Ih], [Ij], [Im], and [Ip], which are also objective compounds of the present invention, were prepared, for example, according to the above process (a).

When used as medicines, the present inventive compounds represented by the general formula [I] given above and their acid addition salts can be administered orally or parenterally. That is, they can be administered orally in usual dosage forms such as tablets, capsules, sirups, suspensions, and solutions or parenterally in the form of injectable liquids such as solutions, emulsions, and suspensions. Further, they can be administered rectally in suppository form and also administered in the form of inhalation sprays as well as in the form of percutaneous agents.

The above-mentioned suitable dosage forms can be prepared by compounding the present active compounds with conventional acceptable carriers, excipients, binders, stabilizers, etc. For use in the form of injections, it is possible to add acceptable buffers, solubilizing aids, isotonic agents, etc. to the present active compounds.

While the dose and the frequency of dosage depend upon the condition, age, and weight of the patient, the dosage form, etc., about 1 to 5000 mg, preferably 10 to 300 mg, of the present active compound is generally administered once or in parts a day for an adult.

Action or Effect of the Invention

It has been revealed that the present inventive compound [I] has pharmacological effects desirable as a curative agent for PAF-induced diseases. That is, the compound [I] exhibits a powerful and selective PAF-antagonism and is excellent in effects also in vivo. The pharamacological effect of the present inventive compound is described below in detail.

Test in vitro for Inhibition of Platelet Aggregation

(A) Inhibition of rabbit platelet aggregation

The inhibition of PAF-induced platelet aggregation was examined by using a platelet-rich plasma (PRP) of rabbit according to the method of Mustard et al. [J.F. Mustard et al., J. Lab. Clin. Med., 64, 548 (1964)], which is an improvement of the method of Born [G.V.R. Born, J. Physiol., London, 162, 67 (1962)]. That is, 80-100 ml of blood per animal was collected from carotid arteries of male rabbits of the Japanese white breed without anesthesia into a polyethylene vessel containing 1/10 the volume of a 3.8% sodium citrate solution. A portion (about 3 ml) of the collected blood was centrifuged at a high speed (11,000 rpm) for 60 seconds, giving a plat let-poor plasma (PPP) as supernatant. The remainder of th blood was centrifuged at a low spe d (1000 rpm) for 10 minut s, giving a platelet-rich plasma (PRP) as sup rnatant.

The degree of platelet aggregation was det rmin d by neph lometry with an aggreg meter (Hematrac r, Niko Bioscience Co.) whil stirring the PRP at 1000 rpm at 37°C. The platelet aggregation activity was expressed in terms of the light transmittance (%), th value of PRP being taken as 0% and the value of PPP as

100%. A portion (0.2 ml) of th PRP was placed in a glass cuvett c ntaining a silic ne-treat d stirring iron rod, and 2 µl of dimethylsulfoxid was add d. After 2 minutes, PAF dissolved in 0.25% BSA physiological saline was added to giv a final PAF concentration f 0.005 µl/ml, and the maximum aggregation was d termined. To examine the inhibitory activity of t st compounds on the platelet aggregation caused by PAF, 2 µl of a dimethylsulfoxide solution of each test comp und was added in place of the dimethylsulf xide. The percentage inhibition by the test compound of PAF-induced platelet aggregation was calculated according to the following equation and the value of IC_{50} was determined.

$$= \left[1 - \frac{\text{Max. aggregation after addition of test compound}}{\text{Max. aggregation after addition of dimethylsulfoxide}} \right] \times 100$$

Results of the test are shown in Table 1.

Table 1

Inhibition of PAF-induced rabbit platelet aggregation

Test compound (compound No.)	IC_{50} value [µg/ml]
2	4.0
3	3.5
7	2.0
8	3.6
9	1.6
15	2.6
18	3.0
24	2.0
25	10
27	0.02
28	0.20
30	4.2
37	0.7
42	2.5
43	1.2
46	1.9
47	1.4
49	2.4
50	4.6
51	1.4
67	0.45
69	0.24
71	0.32

- Cont'd -

Table 1 (Cont'd)

73	0.07
75	0.06
76	0.20
77	0.034
78	0.14
79	0.05
80	0.35
81	0.10
82	0.60
83	0.27
108	0.70
127	1.7
128	4.2
130	4.2
131	0.14
133	0.18
135	0.15
137	0.19
150	0.16
154	2.4
165	0.30
169	0.026
170	0.052
171	4.2
172	0.30
178	1.5
181	5.0

(B) Inhibition of human platelet aggregation

The inhibition of PAF-induc d platelet aggregation was tested by using human PRP. The test was conducted according to th procedure of the above cas of rabbit, thereby evaluating th percentages inhibition and IC_{50} values of test compounds at final PAF concentrations of 0.3 μM and 1 μM. Results of the evaluation are sh wn in Table 2.

Table 2

Inhibition of PAF-induced human platelet aggregation

Test compound (Compound No.)	IC_{50} value (μg/ml)	
	PAF concentration	
	0.3 μM	1 μM
2	5.5	-
3	6.0	-
27	0.2	0.4
28	1.2	2.5
33	5.5	-
108	1.8	6.0

None of the test compounds at a concentration of 10 μg/ml affected at all the aggregation induced by other aggregating agents, e.g. ADP and collagen.

Test in vivo for Inhibition of PAF-Induced

Blood Concentration

Guinea pigs under anesthesia with urethane (6.25 mg/kg injected into the abdominal cavities) were cannulated through carotid arteries and jugular veins. The carotid artery cannulae were used for blood sampling and the jugular vein cannulae for the intravenous injection of test compound and PAF.

Compound No. 27 was suspended in 10% Nikkol® liquid to a concentration of 3 mg/ml, and 1 ml/kg of the resulting suspension was administered through the jugular vein cannulae. Two minutes later, 1 ml/kg of a 0.1 μg/ml PAF solution was administered through the jugular vein cannulae. Then, blood was sampled at times. The blood samples were each centrifuged at 11,000 rpm for 5 minutes and the hematocrit values were measured to determine the maximum increase (blood concentration) in hematocrit value.

For a control, 0.5% methyl cellulose solution was administered in place of compound No. 27.

The percentage inhibition of the PAF-induced blood concentration by compound No. 27 was calculated according to the following equation:

$$\text{Percentage inhibition} = \left[1 - \frac{\text{PAF-induced average maximum increase in hematocrit value in animals injected with compound 27}}{\text{PAF-induced average maximum increase in hematocrit value in control animals}}\right] \times 100$$

The found percentage inhibition was 87%.

Results of the same test on other compounds are shown in Table 3.

Table 3

Inhibition of PAF-induced blood concentration

Test compound (Example No.)	Percentage inhibition	
	Dose 3 mg/kg.iv	Dose 30 mg/kg.iv
2	53%	-
3	-	58%
28	-	92%

Test for inhibition of fatal effect of PAF on mice

Male ICR mice (purchased from Charles River Co.) aged 4 weeks were anesthetized by injecting subcutaneously 100 mg/kg of Isomital® soda (sodium amobarbital supplied by Nippon Shinyaku Co., Ltd.). After 18 minutes, the mice were injected with a test compound or a solvent through tail veins. The test compound was dissolved in a 0.2 M phosphate buffer solution to a concentration of 1 mg/ml and 10 ml/kg of this solution was injected (dose of test compound : 10 mg/kg). Two minutes after this administration, the mice were injected with 10 µg/kg of PAF through tail veins. The PAF was dissolved in physiological saline containing 0.25% of bovine serum albumin to a concentration of 2 µg/ml, and the mice were injected with 5 ml/kg of this solution.

After PAF administration, the mice were observed and the survival rate of mice 2 hours later was determined. The found survival rates were as follows:

Test Compound No.	Survival rate (%)
Control	0
174	80
175	60
182	100

The results of the above tests indicate that the antagonistic action of the present inventive compound [I] on PAF is powerful and highly specific. This action was confirmed by not only in vitro tests but also in vivo tests. Accordingly, the present inventive compound [I] is very useful as a preventive and curative agent for PAF-induced diseases, for example, various kinds of inflammation, circulatory diseases, allergic diseases, and gastrointestinal ulcers.

The present invention is illustrated with reference to the following examples and reference examples, which are not intended to restrict the scope of the invention.

Reference Example 1

Preparation of 2-mercaptoundecanoic acid

(I) Methyl 2-bromoundecanoate $n\text{-}C_9H_{19}COOH \rightarrow n\text{-}C_{10}H_{21}CHBrCOOCH_3$

Undecanoic acid (100 g, 0.54 mol) was added to thionyl chloride (108 ml, 1.48 mol) and this mixture was refluxed for 2 hours. Then, bromine (29 ml, 0.57 mol) was added dropwise over 1.5 hours under reflux. Reflux was continued for 5 additional hours.

The resulting mixture was cooled to room temperature, methanol (250 ml, 6.1 mol) was added dropwise over 30 minutes, and this reaction mixture was left standing overnight. After addition of aqueous NaCl, the product mixture was extracted twice with ether. The extract was washed with aqueous $NaHCO_3$, aqueous Na_2SO_3, and aqueous NaCl, and then dried. The solvent was removed in vacuo, giving crude methyl 2-bromoundecanoate (145 g, 97% yield).

IR (neat) [cm^{-1}]; 2920, 2850, 1736, 1432, 1144

(II) Methyl 2-acetylthioundecanoate $n\text{-}C_9H_{19}CHBrCOOCH_3 \rightarrow n\text{-}C_9H_{19}CH(SCOCH_3)COOCH_3$

Dry dimethylformamide (600 ml) was added to 60% sodium hydride (22.5 g, 0.56 mol) under a stream of nitrogen. The mixture was cooled to 0°C, thioacetic acid (51.6 g, 0.68 mol) was added dropwise at 0 to 10°C, and the mixture was kept between those temperatures for 1 hour. Then crude methyl 2-bromoundecanoate (145 g, 0.52 mol) from above (I) was added dropwise at 0 to 10°C, and the mixture was kept between those temperatures for 2 hours. After addition of aqueous NaCl, the product mixture was extracted twice with ether. The extract was washed with aqueous $NaHCO_3$, aqueous Na_2SO_3, and aqueous NaCl, and dried. The solvent was removed in vacuo and the residue was purified by column chromatography, giving methyl 2-acetylthioundecanoate (108 g, 76% yield).

IR (neat) [cm^{-1}]; 2920, 2860, 1738, 1698, 1435, 1350 1152, 950

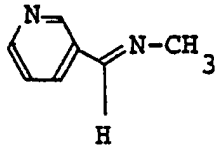
(III) 2-Mercaptoundecanonic acid $n\text{-}C_9H_{19}CH(SCOCH_3)COOCH_3 \rightarrow n\text{-}C_9H_{19}CH(SH)COOH$

Methyl 2-acetylthioundecanoate (122.2 g, 0.44 mol) from above (II) was dissolved in methanol (527 ml). Water (226 ml) and NaOH (67.8 g, 1.67 mol) were added in turn. The mixture was heated under reflux for 2 hours and then cooled. After addition of water, the product mixture was extracted twice with hexane. The aqueous layer was acidified to a pH of 1 to 2 with conc. HCl, and extracted twice with ether. The combined extracts were washed with aqueous NaCl, and dried. The solvents were removed in vacuo, giving 2-mercaptoundecanoic acid (95.54 g, 98% yield).

IR ($CHCl_3$) [cm^{-1}]; 2850, 1705

Reference Example 2

Preparation of N-nicotinylidenemethylamine



Nicotinaldehyde (10.7 g, 0.1 mol) was dissolved in toluene (100 ml). A 40% aqueous methylamin (23.3 g, 0.3 mol) solution was added. This mixture was subjected to azeotropic dehydration for 3 hours. The product mixture was concentrated under reduced pressure, giving N-nicotinylidenemethylamine (11.7 g, 98% yield).

NMR ($CDCl_3$ δ) [ppm]; 3.53 (3H, d, J = 1.7Hz), 7.3-8.85 (5H, m)

Reference Example 3

Preparation f 1-Iodo-2-[2-(1-methylethoxy)ethoxy]ethane

(I) 1-Chloro-2-(2-methanesulfoxy)ethane

2-(2-Chloroethoxy)ethanol (20 g, 0.16 mol) was dissolved in dichloromethane (200 ml), and triethylamine (16.2 g, 0.16 mol) was added. This reaction mixture was cooled with ice and methanesulfonyl chloride (18.3 g, 0.16 mol) was added dropwise over 1 hour. Then the mixture was further stirred for 1 hour while continueing ice-cooling. Saturated aqueous $NaHCO_3$ (40 ml) was added dropwise to the product mixture udner cooling with ice, and the separated aqueous layer was extracted with dichloroethane. The extract was washed with 10% aqueous HCl, saturated aqueous NaCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl in that order, and dried over $MgSO_4$. Then the solvent was removed in vacuo, giving 1-chloro-2-(2-methanesulfoxyethoxy)ethane (33.6 g, 100% yield).

IR ($CHCl_3$) [cm^{-1}]; 1355, 1300, 1170, 1135, 1115, 969, 913

NMR ($CDCl_3$) [δ ppm]; 4.41-4.38 (2H, m), 3.81-3.76 (4H, m), 3.65 (2H, t, J = 5.9 Hz), 3.08 (3H, S)

(II) 1-Chloro-2-[2-(1-methylethoxy)ethoxy]ethane

Dry isopropyl alcohol (12.2 ml, 160 mol) was placed in a dried 4-necked flask and finely-cut pieces of metallic sodium (920 mg, 40 mmol) was added under a stream of nitrogen. The mixture was heated under reflux for 3 hours. Then, heating was stopped and 1-chloro-2-(2-methanesulfoxyethoxy)ethane (8.4 g) was added all at once. After heat generation had ceased, the product mixture was cooled to room temperature, dil. aqueous HCl was added, and the mixture was extracted twice with ether. The extract was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over $MgSO_4$. Then the solvent was removed in vacuo and the residue was distilled under reduced pressure, giving 1-chloro-2-[2-(1-methylethoxy)ethoxy]ethane (3.7 g, 55% yield) at 114 to 121°C under 73 to 83 mmHg.

IR ($CHCl_3$) [cm^{-1}]; 2870, 1460, 1382, 1370, 1335, 1300, 1120, 1090, 970, 912

NMR ($CDCl_3$) [δ ppm]; 3.77 (2H, t, J = 5.9 Hz), 3.68-3.57 (7H, m), 1.17 (6H, d, J = 5.9 Hz)

(III) 1-Iodo-2-[2-(1-methylethoxy)ethoxy]ethane

1-Chloro-2-[2-(1-methylethoxy)ethoxy]ethane (1.0 g, 6.0 mmol) was dissolved in acetone (10 ml), and sodium iodide (1.2 g, 8.0 mmol) was added. The mixture was refluxed for 2 hours and then cooled to room temperature. The reaction mixture was filtered to remove the formed NaCl and the filtrate was evaporated in vacuo.

Water was added to the residue and the mixture was extracted twice with ether. The extract was washed with 5% aqueous Na_2SO_3 and saturated aqueous NaCl, and dried over $MgSO_4$. Then the solvent was removed in vacuo under 20°C and the residue was purified by column chromatography (Si60® hexane-ethyl acetate = 20:1), giving 1-iodo-[2-(2-methylethoxy)ethoxy]ethane (1.0 g, 66% yield).

IR ($CHCl_3$) [cm^{-1}]; 2870, 1465, 1885, 1374, 1340, 1120, 1090, 970

NMR ($CDCl_3$) [δ ppm]; 3.77 (2H, t, J = 6.9 Hz), 3.66-3.57 (6H, m), 3.26 (1H, t, J = 6.9 Hz) 1.17 (6H, d, J = 6.2 Hz)

Reference Example 4

Preparation of 1-chloro-2-(2-t-butyldimethylsilyloxyethoxy)ethane

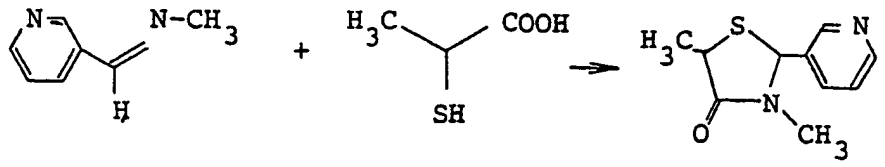
Imidazole (17.8 g, 261 mmol) was dissolved in dimethylformamide (100 ml) and t-butyldimethylsilyl chloride (36.3 g, 241 mmol) was added and stirred. 2-(2-chloroethoxy)ethanol (25.0 g, 200 mmol) was added dropwise over 1 hour under cooling with ice, and the mixture was stirred for 1 further hour, left standing overnight at room temperature, and then poured into saturated aqueous NaCl (500 ml). The resulting mixture was extracted twice with ether. The extract was washed twice with saturated aqueous NaCl, and dried over $MgSO_4$. Then the solvent was removed in vacuo, giving 1-chloro-2-(2-t-butyldimethylsilyloxyethoxy)ethane (47.8 g, 100% yield).

IR ($CHCl_3$) [cm^{-1}]; 2920, 2850, 1460, 1100, 930

NMR ($CDCl_3$) [δ ppm]; 3.94-3.90 (4H, m), 3.79-3.72 (4H, m), 1.05 (9H, s), 0.22 (6H, s)

Example 1

Preparation of 3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 1)



N-Nicotinylidenemethylamine (12.0 g, 0.1 mmol) was dissolved in toluene (100 ml) and thiolactic acid (10.6 g, 0.1 mol) was added. The mixture was subjected to azeotropic dehydration for 3 hours. The product mixture was cooled and washed with 5% aqueous $NaHCO_3$ solution, and dried. The solvent was removed in vacuo. The residue was subjected to recrystallization from ether, giving 3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one (15.6 g, 75% yield).

m.p. 89.5-92°C

IR (nujol) [cm^{-1}]; 1670, 1582, 1017, 719

Example 2

3,5-Dimethyl-2-(3-pyridyl)thiazolidin-4-one (5g) from Example 1 was subjected twice to recrystallization from a 1:1 ethyl acetate-hexane mixture, giving its cis-isomer (compound No. 2). The filtrate was subjected to medium-pressure liquid chromatography (hexane-ethanol) to isolate the trans-isomer (compound No. 3).

cis-Isomer (compound No. 2)

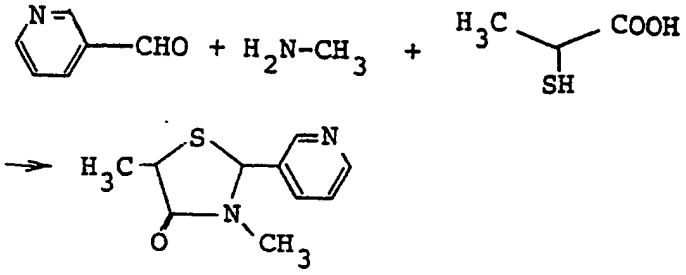
m.p. 98.5-99°C

trans-Isomer (compound No. 3)

m.p. 81-82°C

Example 3

Preparation of 3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 1) (another method)

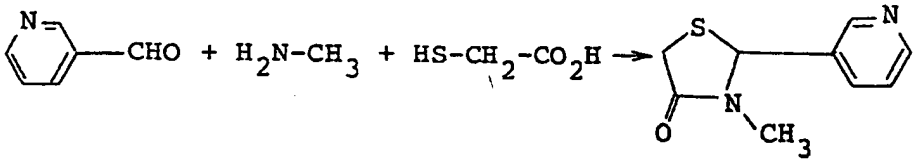


Nicotinaldehyde (10.7 g, 0.1 mol) was dissolved in toluene (100 ml), and a 40% aqueous methylamine (23.3 g, 0.3 mol) solution and thiolactic acid (10.6 g, 0.1 mol) were added. The mixture was subjected to azeotropic dehydration for 3 hours. The product mixture was cooled, washed with 5% aqueous $NaHCO_3$, and dried. The solvent was removed in vacuo, and the residue was subjected to recrystallization from ether, giving 3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one (14.2 g, 68% yield).

m.p. 90-92°C

Example 4

Preparation of 3-methyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 4)

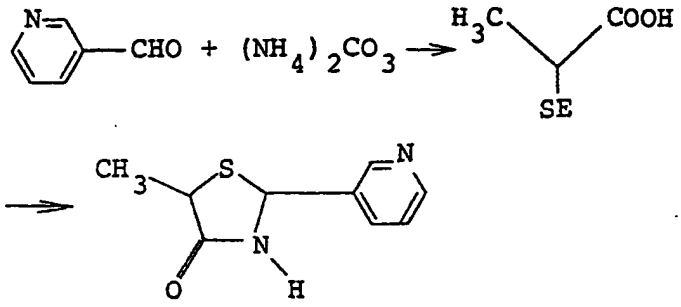


According to the procedure of Example 3, the title compound was prepared by using nicotinaldehyde, a

40% aqueous methylamin solution, and thioglyc lic acid as charg stock.
m.p. 96.5-97.5°C
IR (nujol) [cm^{-1}]; 1670, 1583, 1236, 1109, 1005, 717

Example 5

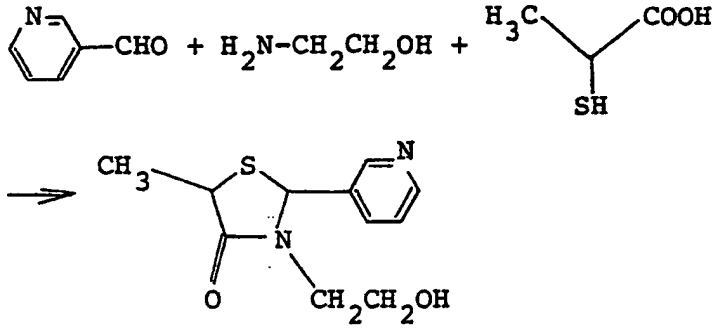
Preparation of 5-methyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 5)



According to the procedure of Example 3, the title compound was prepared by using nicotinaldehyde, ammonium carbonate, and thiolactic acid as charge stock.
m.p. 109.5-110.5°C
IR (nujol) [cm^{-1}]; 1680

Example 6

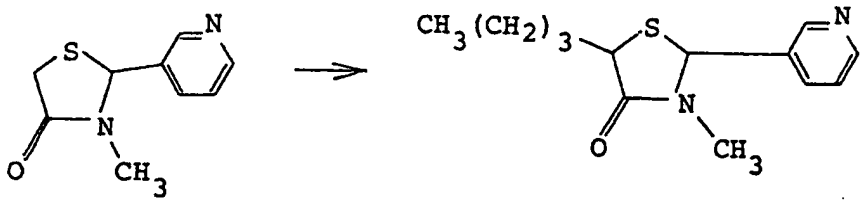
Preparation of 3-(2-hydroxyethyl)-5-methyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 6)



According to the procedure of Example 3, the title compound was prepared by using nicotinaldehyde, ethanolamine, and thiolactic acid as charge stock.
NMR (δ, $CDCl_3$) [ppm]; 1.63 (1H, d, J = 6,8 Hz), 1.66 (2H, d, J = 6.8 Hz), 2.8-4.2 (6H, m), 5.83 (1H, s)
IR ($CHCl_3$) [cm^{-1}]; 3400, 2940, 1670, 1593, 1580, 1450, 1360, 1070.

Example 7

Preparation of 5-butyl-3-methyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 7)



Dry diisopropylamine (1 ml, 5.7 mmol) was added to dry tetrahydrofuran (3 ml), and a butyllithium solution (3.9 ml, 6.2 mmol) in hexane was added dropwise at -40°C, the mixture was kept at -10°C for 1 hour. A solution of 3-methyl-2-(3-pyridyl)thiazolidin-4-one (1 g, 5.2 mmol) in dry tetrahydrofuran (7 ml) was added dropwise to the mixture at -20 to -10°C. After this reaction mixture had been kept between those temperatures for 1 hour, there were added at -10°C 1-bromobutane (0.78 g, 5.7 mmol) dissolved in tetrahydrofuran (2 ml), sodium iodide (0.77 g, 5.2 mmol), and hexamethylphosphorotriamide (1 ml). This reaction mixture was kept at room temperature for 2 hours. The resulting mixture, after addition of a phosphate buffer (pH 7.0), was extracted with ethyl acetate. The extract was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated by evaporation under reduced pressure. The residue was chromatographed on silica gel (hexane-ethyl acetate), giving 5-butyl-3-methyl-2-(3-pyridyl)thiazolidin-4-one (250 mg, 20% yield).

NMR ($CDCl_3$) δ [ppm]; 0.93 (3H, t, J = 7.0 Hz), 1.2-2.3 (6H, m), 2.74 (3H, m), 3.9-4.3 (1H, m), 5.4-5.5 (1H, m)
IR ($CHCl_3$) [cm^{-1}]; 2925, 2855, 1670, 1590, 1578, 1390, 1303, 1020

Example 8

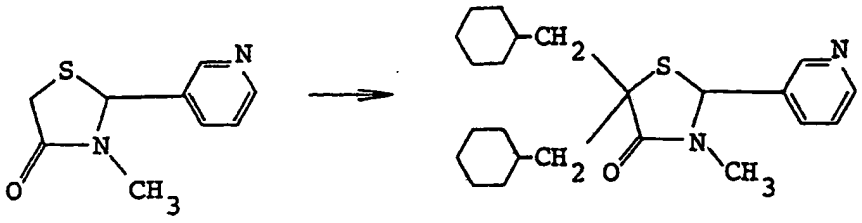
Preparation of 5,5,3-trimethyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 8)

Dry diisopropylamine (0.95 ml, 5.3 mmol) was added to dry tetrahydrofuran (3 ml). Further a butyllithium solution (3.6 ml, 5.8 mmol) in hexane was added dropwise at -40°C. The mixture was kept at -10°C for 1 hour. Then a solution of 3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one (1 g, 4.8 mmol) in dry tetrahydrofuran (7 ml) was added dropwise at -20 to -10°C. After this reaction mixture had been kept between those temperatures for 1 hour, methyl iodide (0.75 g, 5.3 mmol) dissolved in dry tetrahydrofuran (2 ml) was added at -20 to -10°C. This reaction mixture was heated for 2 hours up to 0°C and then kept at the same temperature for 2 hours. The resulting mixture, after addition of a phosphate buffer (pH 7.0), was extracted with ethyl acetate. The extract was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure, and subjected to medium-pressure liquid chromatography (hexane-acetone) and then to recrystallization from a 1:1 ether-hexane mixture, giving 5,5,3-trimethyl-2-(3-pyridyl)thiazolidin-4-one (0.42 g, 39% yield).

NMR ($CDCl_3$) δ [ppm]; 1.62 (3H, s), 1.68 (3H, s), 2.74 (3H, s), 5.51 (1H, s)
IR (nujol) [cm^{-1}]; 1668, 1590, 1390, 1310, 1135, 1071, 1021

Example 9

Preparation of 5,5-di(cyclohexylmethyl)-3-methyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 184)

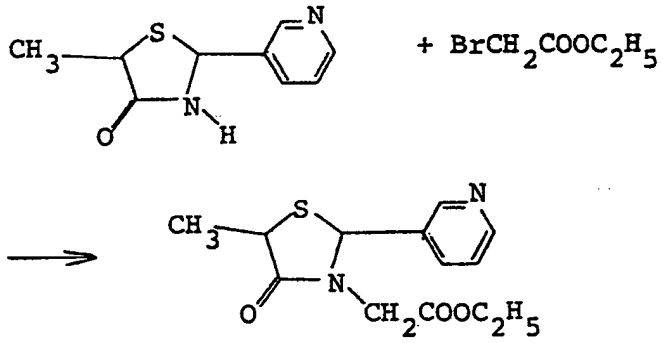


Dry diisopropylamine (2.76 ml, 15.8 mmol) was added to dry tetrahydrofuran (9 ml). Further a n-butyllithium solution (10.6 ml, 16.2 mmol) in hexane was added dropwise at -20 to -30°C. The mixture was kept between those temperatures for 1 hour. Then a solution of 3-methyl-2-(3-pyridyl)thiazolidin-4-one (3 g, 15.4 mmol) in dry tetrahydrofuran was added dropwise at -78°C. After this reaction mixture had been kept at the same temperature for 1 hour, bromomethylcyclohexane (3.01 g, 17.0 mmol) and sodium iodide (2.31 g, 15.4 mmol) were added at -78°C. This reaction mixture was heated up to room temperature and kept standing overnight. The resulting mixture, after addition of aqueous NaCl, was extracted with ethyl acetate. The extract was washed with aqueous NaCl, dried, and the solvent was removed in vacuo. The residue was chromatographed on silica gel, giving 5,5-di(cyclohexylmethyl)-3-methyl-2-(3-pyridyl)thiazolidin-4-one (250 mg, 4.2% yield).

IR ($CHCl_3$) [cm^{-1}]; 2920, 1675, 1640, 1390

Example 10

Preparation of 3-ethoxycarbonylmethyl-5-methyl-2-(3-pyridyl)thiazolidin-4-one (compound Nos. 9, 10)



5-Methyl-2-(3-pyridyl)thiazolidin-4-one (10 g, 51.5 mmol) and ethyl bromoacetate (6.85 ml, 61.8 mmol) were dissolved in dry dimethylformamide (50 ml), and 60% sodium hydride (2.16 g, 54.1 mmol) was added in limited amounts to the solution at 0 to 10°C. This reaction mixture was kept between those temperatures for 1 hour. The mixture, after addition of aqueous NaCl, was extracted with ethyl acetate. The extract was washed with aqueous NaCl, dried, and the solvent was removed in vacuo. The residue was chromatographed on silica gel, giving the cis-isomer (5.8 g) (compound No. 9) and the trans-isomer (2.1 g) (compound No. 10) of the title compound (55% yield).

Compound No. 9 : cis-isomer

NMR ($CDCl_3$, δ) [ppm]; 1.24 (3H, t, J = 7.2 Hz), 1.67 (3H, d, J = 7.1 Hz), 5.81 (1H, s)

IR ($CHCl_3$) [cm^{-1}]; 2950, 1740, 1683, 1587, 1575, 1441, 1370, 1014

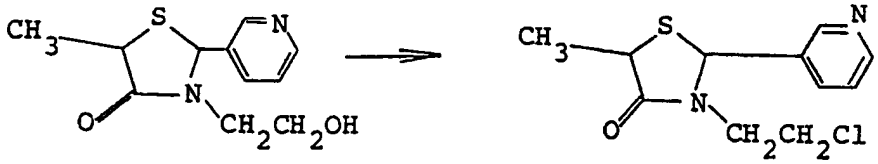
Compound No. 10 : trans-isomer

NMR ($CDCl_3$, δ) [ppm]; 1.25 (3H, t, J = 7.2 Hz), 1.68 (3H, d, J = 7.1 Hz), 5.83 (1H, d, J = 1.7 Hz)

IR ($CHCl_3$) [cm^{-1}]; 2950, 1739, 1685, 1585, 1572, 1370, 1345, 1012

Example 11

Preparation of 3-(2-chloroethyl)-5-m thyl-2-(3-pyridyl)thiazolidin-4-one (compound Nos. 11, 12)



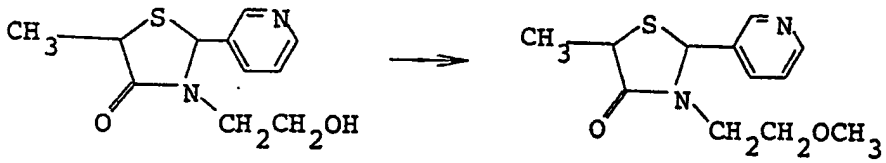
3-(2-Hydroxyethyl)-5-methyl-2-(3-pyridyl)thiazolidin-4-one (18.75 g, 78.7 mmol) was dissolved in methylene chloride (200 ml). Pyridine (9.55 ml, 118 mmol) was added and further, thionyl chloride (20 ml, 274 mmol) was added dropwise over 2 hours at 0 to 5°C. This reaction mixture was kept between those temperatures for 5 hours. The resulting mixture was washed with aqueous $NaHCO_3$ and aqueous NaCl, dried, and the solvent was removed in vacuo. The residue was chromatographed on silica gel and upon recrystallization from hexane-ether, gave 2,5-cis-3-(2-chloroethyl)-5-methyl-2-(3-pyridyl)thiazolidin-4-one (7.11 g) and 2,5-trans-3-(2-chloroethyl)-5-methyl-2-(3-pyridyl)thiazolidin-4-one (3.11 g), (51% yield).

Compound No. 12 : cis-isomer, m.p. 76-77°C

Compound No. 11 : trans-isomer, m.p. 112.5-113.5°C

Example 12

Preparation of 3-(2-methoxyethyl)-5-methyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 13)



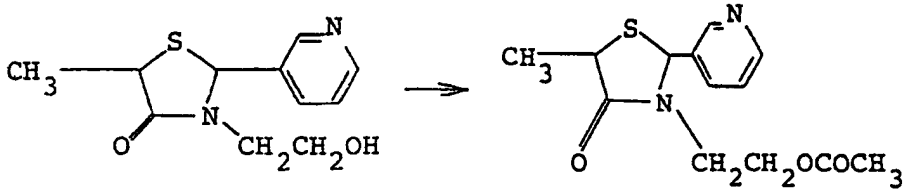
Methyl iodide (0.72 g, 5.0 mmol) was added to a solutoin of 3-(2-hydroxyethyl)-5-methyl-2-(3-pyridyl)thiazolidin-4-one (1 g, 4.2 mmol) in dry dimethylformamide (5 ml), and 40% sodium hydride (176 mg, 4.4 mmol) was added in limited amounts to the mixture under cooling with ice. Then, cooling with ice was continued for 1 hour. The product mixture was poured into aqueous NaCl, and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated and subjected to medium-pressure chromatography (hexane-acetone), giving 3-(2-methoxyethyl)-5-methyl-2-(3-pyridyl)thiazolidin-4-one (0.51 g, 48% yield).

NMR ($CDCl_3$) δ [ppm]; 1.62 (0.75 H, d, J = 7.1 Hz), 1.66 (2.5 H, d, J = 7.1 Hz), 3.28 (2.25 H, s), 3.3 (0.75 H, s), 5.85 (1H, s)

IR ($CHCl_3$) [cm^{-1}]; 2935, 1670, 1589, 1576, 1445, 1408, 1300, 1113

Example 13

Preparation of 3-(2-acetoxyethyl)-5-methyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 14)



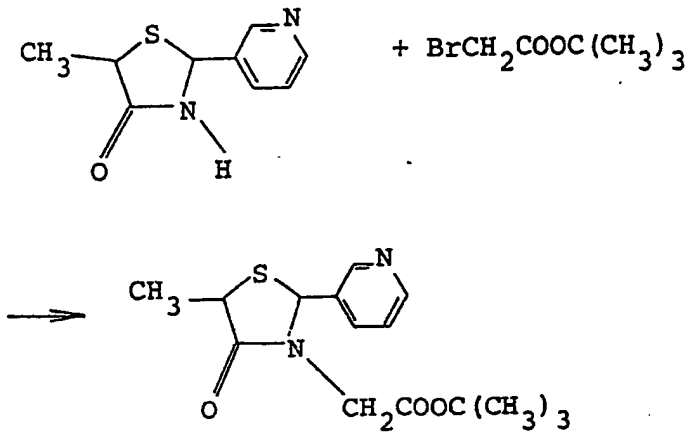
Pyridine (0.5 ml) was added to a solution of 3-(2-hydroxyethyl)-5-methyl-2-(3-pyridyl)thiazolidin-4-one (0.5 g, 2.1 mmol) in acetic anhydride (2 ml) under cooling with ice. This cooling with ice was further continued for 2 hours. The product mixture was concentrated by evaporation under reduced pressure, and subjected to medium-pressure chromatography (hexane-acetone), giving 3-(2-ac toxyethyl)-5-methyl-2-(3-pyridyl)thiazolidin-4-on (0.45 g, 77% yield).

NMR ($CDCl_3$) δ [ppm]; 1.62 (1H, d, J = 7.1 Hz), 1.66 (2H, d, J = 7.1 Hz), 2.06 (3H, s), 5.74 (1H, s)

IR ($CHCl_3$) [cm^{-1}]; 2960, 1740, 1693, 1590, 1579, 1350, 1020

Example 14

Preparation of 3-t-butyloxycarbonylmethyl-5-methyl-2-(3-pyridyl)thiazolidin-4-one (compound Nos. 15, 16)

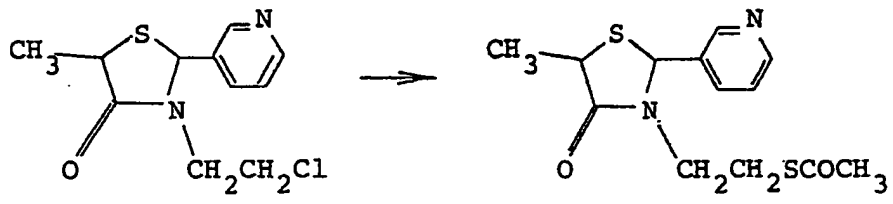


According to the procedure of Example 10, the trans-isomer (compound No. 15) and the cis-isomer (compound No. 16) of the title compound were prepared by using 5-methyl-2-(3-pyridyl)thiazolidin-4-one, t-butyl bromoacetate, and sodium hydride as charge stock.

Compound No. 15 : trans-isomer, m.p. 132-133°C
IR (nujol) [cm^{-1}]; 1738, 1690, 1679, 1572, 1260, 1164
Compound No. 16 : cis-isomer, m.p. 108-108.5°C
IR (nujol) [cm^{-1}]; 1738, 1681, 1694, 1591, 1575, 1247, 1170

Example 15

Preparation of 3-(2-Acetylthioethyl)-5-methyl-2-(3-pyridyl)thiazolidin-4-one (compound Nos. 17, 18)



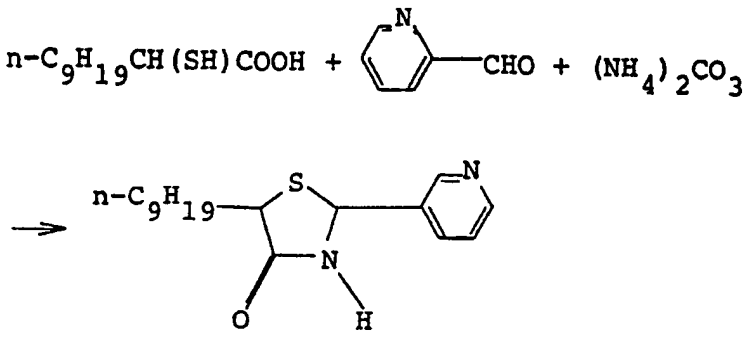
Potassium thioacetate (0.53 g, 4.7 mmol) was added to a solution of 2,5-trans-3-(2-chloroethyl)-5-methyl--2-(3-pyridyl)thiazolidin-4-one (1 g, 3.9 mmol) in dimethylforamide (5 ml) and the mixture was stirred for 1 hour under cooling with ice. The product mixture, after addition of aqueous $NaHCO_3$, was extracted with ethyl acetate. The extract was washed with aqueous NaCl, dried, and the solvent was removed in vacuo. The residue was chromatographed on silica gel, giving 2,5-trans-3-(2-acetylthioethyl)-5-methyl-2-(3-pyridyl)thiazolidin-4-one (0.85 g, 78% yield).

The cis-isomer also was prepared as stated above.

Compound No. 17 : trans-isomer, m.p. 60-62°C
Compound No. 18 : cis-isomer, m.p. 55-56.5°C

Exampl 16

Preparation of 5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (c mpound No. 19)

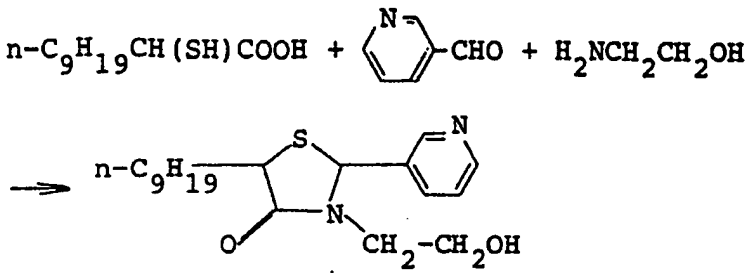


2-Mercaptoundecanoic acid (20 g, 91.6 mmol), nicotinaldehyde (8.64 ml, 91,6 mmol), and $(NH_4)_2CO_3$ (3.3 g, 34.3 mmol) were added to benzene (300 ml), and subjected to azeotropic dehydration for 2 hours. After the reaction mixture was cooled, ($(NH_4)_2CO_3$ (3.3 g, 34.3 mmol) was added at 30-40°C, and the mixture was subjected to azeotropic dehydration. Then the solvent was removed under reduced pressure. The residue was chromatographed on silica gel, and upon recrystallization from ether-hexane, gave 5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (16.7 g, 59% yield).

m.p. 90-95°C

Example 17

Preparatoin of 3-(2-hydroxyethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (compound No. 20)

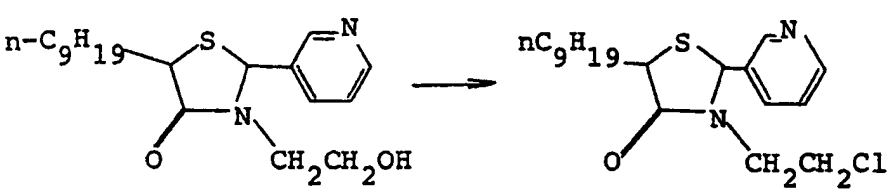


2-Mercaptoundecanoic acid (7 g, 32.1 mmol), nicotinaldehyde (3.03 ml, 32.1 mmol), and ethanolamine (1.93 ml, 32.1 mmol) were added to toluene, (100 ml) and subjected to azeotropic dehydration for 1 hour. The product mixture was cooled and evaporated under reduced pressure to remove the solvent. The residue was purified by column chromatography, giving 3-(2-hydroxyethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (8.17 g, 73% yield).

NMR ($CDCl_3$, δ) [ppm]; 0.85-0.9 (3H, m), 2.9-3.01 (1H, m), 3.65-3.80 (3H, m), 3.97-4.01 (0.7H, m), 4.02-4.07 (0.3H, m), 5.78 (0.3H, d, J = 2.0 Hz), 5.80 (0.7H, s)

Example 18

Preparatoin of 3-(2-chloroethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (compound Nos. 21, 22)



Triphenylphosphine (3.44 g, 13 mmol) was add d to a mixture f 3-(2-hydroxyethyl)-5-(n-nonyl)-2-(3-pyri-

dyl)thiazolidin-4-one (3.49 g, 10 mm l) and carbon tetrachl ride (20 ml) with stirring at ro m temperature. Th n the mixture was refluxed with stirring for 2.5 h urs.

The product mixtur was cooled and filter d to remove the formed crystalls. The filtrate was con ntrated and chromat graphed, giving the cis-isom r (0.55 g) and trans-isomer (1.46 g) f the title c mpound and a mixture of two isomers (0.94 g) (t tal 2.95 g, 80% yield).

cis-isomer (compound No. 21)

IR ($CHCl_3$) [cm^{-1}]; 2915, 2850, 1675, 1590, 1580, 1350

NMR (δ, $CDCl_3$, ppm); 2.99 (1H, ddd, J = 14.52, 7.92 and 5.28 Hz), 3.49 (1H, dt, J = 11.55 and 5.28 Hz), 3.72 (1H, ddd, J = 11.55, 7.92 and 5.28 Hz), 3.95 (1H, dt, J = 14.52 and 5.28 Hz), 4.01 (1H, dd, J = 9.90 and 2.97 Hz), 5.86 (1H, s)

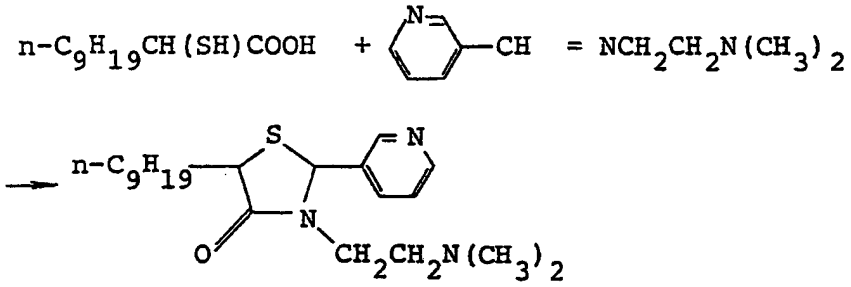
trans-isomer (compound No. 22)

IR ($CHCl_3$) [cm^{-1}]; 2920, 2850, 1678, 1590, 1580, 1355

NMR (δ, $CDCl_3$, ppm); 2.97 (1H, ddd, J = 14.52, 8.24 and 4.95 Hz), 3.51 (1H, ddd, J = 11.54, 5.28 and 4.95 Hz), 3.74 (1H, ddd, 11.54, 8.24 and 4.95 Hz), 3.98 (1H, ddd, J = 9.90, 3.63 and 1.64 Hz), 5.85 (1H, d, J = 1.64 Hz)

Example 19

Preparation of 3-(2-dimethylaminoethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (compound No. 23)

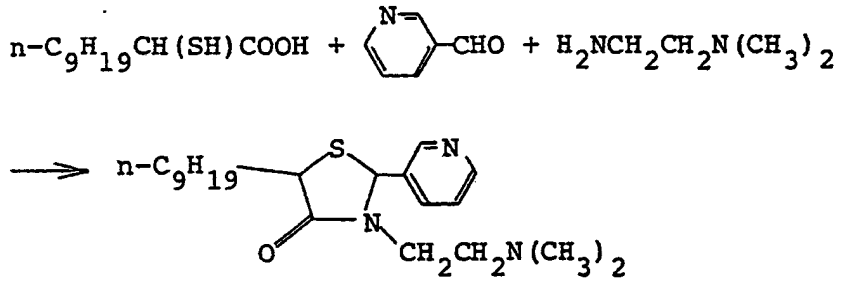


2-Mercaptoundecanoic acid (2 g, 9.16 mmol) and N-nicotinylidene-N',N'-dimethylethylenediamine (1.62 g, 9.16 mmol) were dissolved in toluene (50 ml), and subjected to azeotropic dehydration for 2 hours. The solvent was removed from the product mixture by evaporation under reduced pressure. The residue was purified by column chromatography, giving 3-(2-dimethylaminoethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (3.1 g, 90% yield).

IR ($CHCl_3$) [cm^{-1}]; 2850, 1660, 1577, 1408

Example 20

Preparatoin of 3-(2-dimethylaminoethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (compound No. 23)

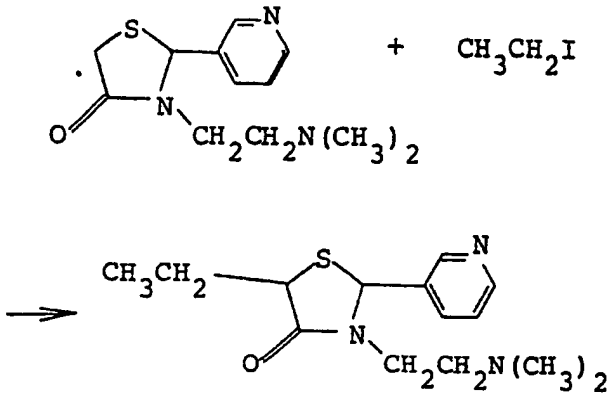


2-M rcaptound canoic acid (5.0 g, 22.9 mmol), pyridin -3-aldehyde (2.16 ml, 22.9 mmol), and N-dimethylaminoethylamine (2.51 ml, 22.9 mmol) were dissolved in toluene (100 ml), and subj cted to azeotropic dehydration for 2 hours. The s lvent was removed from th pr duct mixture by evaporation under reduced pr ssure. Th residu was purified by column chromatography, giving 3-(2-dimethylami-

noethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (7.9 g, 91% yield).
IR ($CHCl_3$) [cm^{-1}]; 2850, 1660, 1577, 1408

Example 21

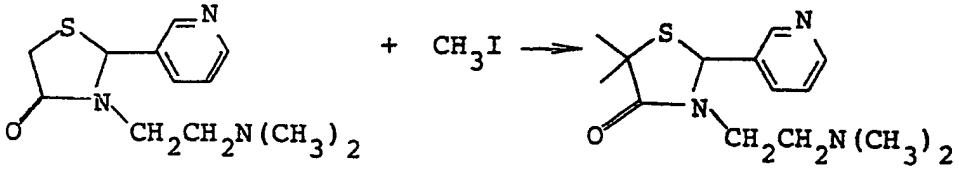
Preparation of 5-ethyl-3-(2-dimethylamino thyl)-2-(3-pyridyl)thiazolidin-4-one (compound No. 24)



n-Butyllithium solution (5 ml, 8 mmol) in hexane was added dropwise to a solution of diisopropylamine (1.42 ml, 7.96 mmol) in dry tetrahydrofuran at -30 to -40°C. The mixture was kept between those temperatures for 1 hour and then cooled to -78°C. Thereto was added dropwise a solution of 3-(2-dimethylaminoethyl)-2-(3-pyridyl)thiazolidin-4-one (2 g, 7.96 mmol) in dry tetrahydrofuran (10 ml). This reaction mixture was kept at that temperature for 1 hour. Then, ethyl iodide (1.24 g, 7.96 mmol) was added, and this reaction mixture was slowly warmed up to room temperature and maintained there for 30 minutes. The resulting mixture, after addition of aqueous NaCl, was extracted with ethyl acetate. The extract was washed with aqueous NaCl, dried, and concentrated by evaporation under reduced pressure. The residue was purified by column chromatography, giving 5-ethyl-3-(2-dimethylaminoethyl)-2-(3-pyridyl)thiazolidin-4-one (1.84 g, 83% yield).
NMR (CDCl, δ) [ppm]; 1.06 (3H, t, J = 7.3 Hz), 2.15 (6H, s), 3.75-3.85 (1H, m), 4.00-4.05 (1H, m), 5.86 (1H, d, J = 2.0 Hz)

Example 22

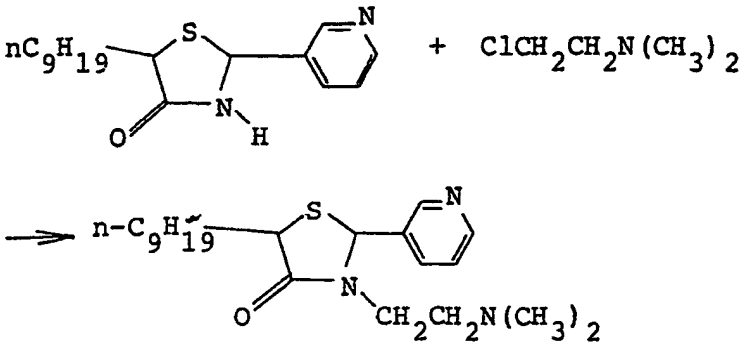
Preparation of 5,5-dimethyl-3-(2-dimethylaminoethyl)-2-(3-pyridyl)thiazolidin-4-one (compound No. 25)



A n-butyllithium solution (10 ml, 16 mmol) in hexane was added to dropwise to a solution of diisopropylamine (2.84 ml, 15.9 mmol) in dry tetrahydrofuran (6 ml) at -20 to -30°C. The mixture was kept between those temperatures for 1 hour and then cooled to -78°C. Thereto was added dropwise a solution of 3-(2-dimethylaminoethyl)-2-(3-pyridyl)thiazolidin-4-one (2 g, 7.96 mmol) in dry tetrahydrofuran (10 ml). The resulting mixture was kept at -78°C for 1 hour. After addition of methyl iodide (2.26 g, 15.9 mmol), this reaction mixture was slowly warmed up to the room temperature and allowed to stand overnight. The resulting mixture, after addition of aqueous NaCl, was extracted with ethyl acetate. The extract was washed with aqueous NaCl, dried, and the solvent was removed in vacuo. The residue was purified by column chromatography, giving 5,5-dimethyl-3-(2-dimethylaminoethyl)-2-(3-pyridyl)thiazolidin-4-one (257 mg, 12% yield).
m.p. 67-70°C

Example 23

Preparation of 3-(2-dimethylaminoethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (comp und No. 23)



K_2CO_3 (0.9 g, 6.52 mmol) and 2-dimethylaminoethyl chloride hydrochloride (0.47 g, 3.26 mmol) were added to a solution of 5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (1 g, 3.26 mmol) in dry dimethylformamide (10 ml). The mixture was kept at 50°C for 10 hours. The resulting mixture, after addition of aqueous NaCl, was extracted with ethyl acetate. The extract was washed with aqueous NaCl, dried, and the solvent was removed in vacuo. The residue was purified by chromatography on silica gel, giving 3-(2-dimethylaminoethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (0.41 g, 33% yield).

IR ($CHCl_3$) [cm^{-1}]; 2850, 1660, 1578, 1407

Example 24

Preparation of 3-(2-acetylaminoethyl)-2-(3-pyridyl)-5-(n-nonyl)thiazolidin-4-one (compound No. 26)

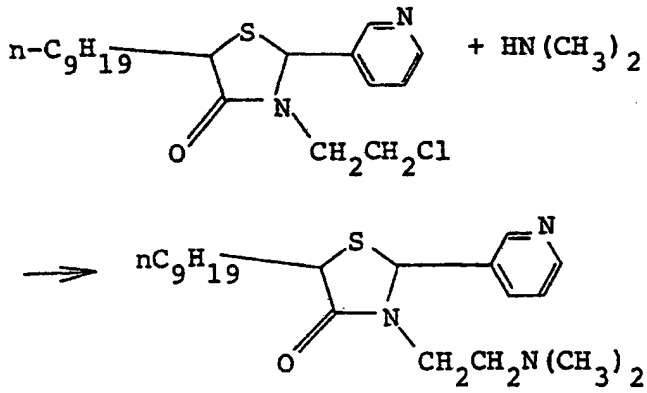
Acetic anhydride (0.2 g) was added dropwise to a solution of 3-(2-aminoethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (0.50 g, 1.43 mmol) in pyridine (2 ml) with stirring under cooling with ice. The mixture was left standing overnight at room temperature. To this solution was added saturated aqueous $NaHCO_3$ (30 ml), and the mixture was extracted with benzene. After drying of the extract, the solvent was removed therefrom by evaporation under reduced pressure, giving the intended 3-(2-acetylaminoethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (0.52 g, 92% yield) in oily form.

IR ($CHCl_3$) [cm^{-1}]; 3430, 2920, 2850, 1665, 1590, 1580, 1365

NMR (δ, $CDCl_3$ ppm); 1.95 (3H, s), 3.93 (0.45H, dd, 990 and 3.63 Hz), 4.03 (0.55H, ddd, 9.24, 3.63 and 1.65 Hz), 5.75 (0.55H, d, 1.65 Hz), 5.76 (0.45H, s), 6.06-6.11 (1H, m)

Example 25

Preparation of 3-(2-dimethylaminoethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (trans-isomer) (compound No. 27)



A 50% aqueous dimethylamine solution (1.0 ml, 11 mmol) was added to a soluti n of trans-isomer (128 mg, 0.35 mmol) of 3-(2-chloroethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one in dimethylsulfoxide (3 ml). The

mixture, placed in a sealed tube, was heated at 100°C for 2 hours. After removal of the solvent by evaporation under reduced pressure, the residue was dissolved in chloroform (30 ml). The s lution was washed twic with saturated aqueous $NaHCO_3$ and dried. Removal of the chloroform gave the intended trans-isomer (131 mg, 100% of theoretical) of 3-(2-dimethylaminoethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-on in olly form.

IR ($CHCl_3$) [cm^{-1}]; 2930, 2860, 1670, 1580, 1355

NMR (δ, $CDCl_3$, ppm); 2.15 (6H, s), 2.24 (1H, dt, 12.87 and 5.61 Hz), 2.46 (1H, ddd, 12.87, 7.20 and 5.94 Hz), 2.69 (1H, ddd, 14.19, 7.20 and 5.61 Hz), 3.80 (1H, ddd, 14.19, 5.94 and 5.61 Hz), 4.03 (1H, ddd, 8.58, 3.96 and 1.98 Hz), 5.86 (1H, d, 1.98 Hz)

Example 26

Isolation-Purification of trans-isomer and cis-isomer

3-(2-Dimethylaminoethyl)-5-(n-nonyl)-2-(3-pyridyl)thiazolidin-4-one (7.9 g) prepared in Example 2 was subjected to medium-pressure liquid chromatography (column size : 40 mm x 500 mm, Silica gel-60®, carrier : hexane : ethanol : aqueous ammonia = 3000 : 300 : 50), giving the trans-isomer (1.42 g), the cis-isomer (3.42 g), and their mixture (2.77 g).

trans-isomer (compound No. 27)

IR ($CHCl_3$) [cm^{-1}]; 2930, 2860, 1670, 1580, 1355

NMR (δ, $CDCl_3$ ppm); 2.15 (6H, s), 40-40.6 (1H, m), 5.86 (1H, d, J = 2.0 Hz)

cis-isomer (compound No. 28)

IR ($CHCl_3$) [cm^{-1}]; 2930, 2860, 1670, 1590, 1360

NMR (δ, $CDCl_3$ ppm); 2.13 (6H, s), 3.97 (1H, dd, J = 3.7 and 9.8 Hz), 5.84 (1H, s)

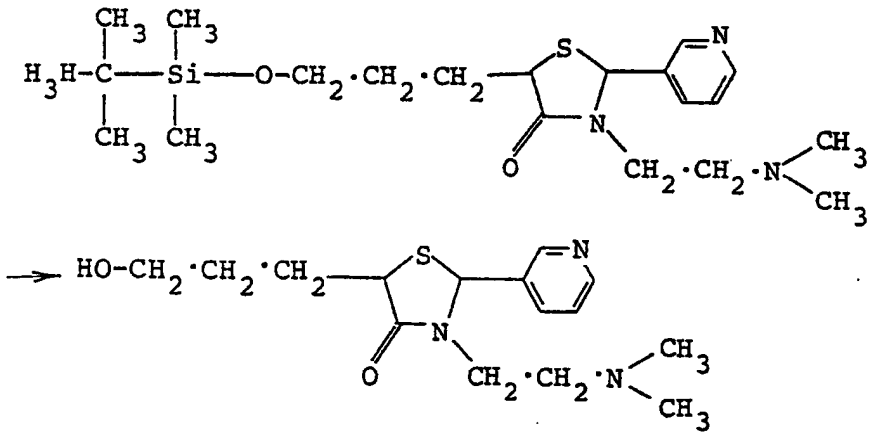
A 5% HCl-Isopropanol mixture (5 g, 7 mmol) was added to a portion (1 g, 2.65 mmol) of the obtained trans-isomer, and stirred for 1 hour at room temperature. The solvent was removed by evaporation under reduced pressure. The residue, subjected to recrystallization from a 1 : 3 ethanol-hexane mixture (5 ml), gave the hydrochloride of the trans-isomer (compound No. 173) (1.02 g, 85% yield).

m.p. 175.5-178°C

IR (KBr) [cm^{-1}]; 2920, 2850, 2660, 1670, 1460

Example 27

Preparation of 3-dimethylaminoethyl-5-(3-hydroxypropyl)-2-(3-pyridyl)thiazolidin-4-one (compound No. 129).



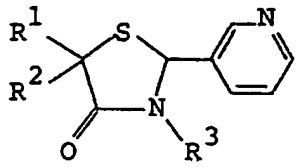
A 1M solution (15 ml) of tetrabutylammonium fluoride in tetrahydrofuran was added dropwise to a solution of 3-dimethylaminoethyl-5-(3-t-butyldimethylsilyloxypropyl)-2-(3-pyridyl)thiazolidin-4-one (2.6 g, 6.02 mmol) in dry tetrahydrofuran (12 ml) under cooling with ice. Then the mixture was stirred at room temperature for 2 hours to complete the reaction. Saturated aqueous $NaHCO_3$ (10 ml) was added dropwise to the product mixture, and the resulting aqueous layer was extracted 6 times with ethyl acetate. The extract wad dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residual crude product was purified by medium-pressure liquid chromatography (Si-60® Art. 9385, eluent : hexane : ethanol: aqueous ammonia = 3000 : 400 : 50), giving 3-dimethylaminoethyl-5-(3-hydroxypropyl)-2-(3-pyridyl)thiazolidin-4-one (1.7 g, 88% yield).

IR ($CHCl_3$) [cm^{-1}]; 3400 (br), 1670, 1595, 1580, 1360

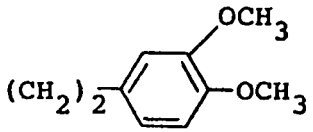
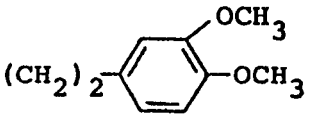
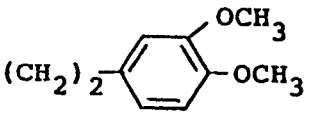
NMR ($CDCl_3$) [δ ppm]; 2.16 (6H, s), 4.10-4.15 (1H, m), 5.86 (1H, d, J = 2 Hz)

Example 28

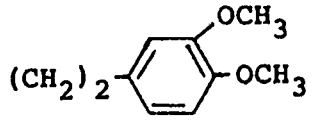
Compounds shown in th following table were prepared according to the procedure of Exampl s 1-26. In the table, R^1, R^2 and R^3 are substituents shown in the following formula:



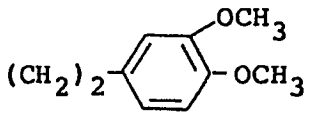
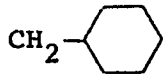
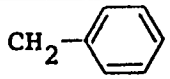
In the row of "Configuration" in the table, "trans" means that the 2- and 5-positional substituents on the thiazolidin-4-one ring are in the configuration of trans to each other; "cis" means that these substituents are in the configuration of cis to each other; and m means a trans-cis mixture.

Compound No.	R_1	R_2	R_3	Configuration
29	H	H		-
30	CH_3	"	CH_2CH_3	m
31	"	"	$CH_2CH=CH_2$	trans
32	"	"	"	cis
33	"	"	$CH_2C\equiv CH$	trans
34	"	"	"	cis
35	"	"	$(CH_2)_2$	trans
36	"	"	"	cis
37	"	"		trans
38	"	"		cis

- Cont'd -

39	CH_3	H	$(CH_2)_3OCH_3$	m
40	"	"	$CH_2CON(CH_3)_2$	trans
41	"	"	"	cis
42	CH_2CH_3	"	CH_3	m
43	$(CH_2)_2CH_3$	"	"	m
44	$CH_2CH(CH_3)_2$	"	"	m
45	$CH(CH_3)CH_2CH_3$	"	"	m
46	$(CH_2)_4CH_3$	"	"	m
47	$(CH_2)_5CH_3$	"	"	m
48	$(CH_2)_8CH_3$	"	"	m
49	"	"	"	trans
50	"	"	"	cis
51	$(CH_2)_9CH_3$	"	"	m
52	$(CH_2)_8CH_3$	"		trans
53	"	"	"	cis

- Cont'd -

54	$(CH_2)_8CH_3$	H	$CH_2COOC_2H_5$	trans
55	"	"	"	cis
56	"	"	$(CH_2)_2COOC_2H_5$	trans
57	"	"	"	cis
58	$(CH_2)_{15}CH_3$	"		trans
59	"	"	"	cis
60		"	CH_3	m
61		"	"	m
62	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	"	
63	$CH_2CH=CH_2$	H	"	m
64	$CH_2C\equiv CH$	"	"	m
65	CH_3	H	$CH_2CH_2CH_2N(CH_3)_2$	trans
66	"	"	"	cis

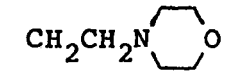
- Cont'd -

67	$n\text{-}C_3H_7$	H	$CH_2CH_2N(CH_3)_2$	trans
68	"	"	"	cis
69	$n\text{-}C_4H_9$	"	"	trans
70	"	"	"	cis
71	$n\text{-}C_5H_{11}$	"	"	trans
72	"	"	"	cis
73	$n\text{-}C_6H_{13}$	"	"	trans
74	"	"	"	cis
75	$n\text{-}C_7H_{15}$	"	"	trans
76	"	"	"	cis
77	$n\text{-}C_8H_{17}$	"	"	trans
78	"	"	"	cis
79	$n\text{-}C_{10}H_{21}$	"	"	trans
80	"	"	"	cis
81	$n\text{-}C_{11}H_{23}$	"	"	trans
82	"	"	"	cis

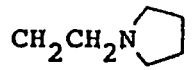
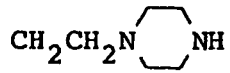
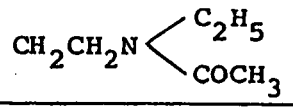
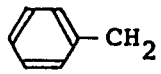
- Cont'd -

83	$n\text{-}C_{12}H_{25}$	H	$CH_2CH_2N(CH_3)_2$	trans
84	"	"	"	cis
85	$n\text{-}C_{13}H_{27}$	"	"	trans
86	"	"	"	cis
87	$n\text{-}C_{14}H_{29}$	"	"	trans
88	"	"	"	cis
89	$n\text{-}C_{15}H_{31}$	"	"	trans
90	"	"	"	cis
91	$n\text{-}C_{16}H_{33}$	"	"	trans
92	"	"	"	cis
93	$n\text{-}C_{17}H_{35}$	"	"	trans
94	"	"	"	cis
95	$n\text{-}C_{18}H_{37}$	"	"	trans
96	"	"	"	cis
97	$n\text{-}C_{19}H_{39}$	"	"	trans
98	"	"	"	cis

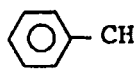
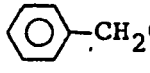
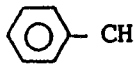
- Cont'd -

99	$n\text{-}C_{20}H_{41}$	H	$CH_2CH_2N(CH_3)_2$	trans
100	"	"	"	cis
101	CH_3	"		trans
102	"	"	"	cis
103	$n\text{-}C_3H_7$	"	$CH_2CH_2CH_2N(CH_3)_2$	trans
104	"	"	"	cis
105	$n\text{-}C_6H_{13}$	"	"	trans
106	"	"	"	cis
107	$n\text{-}C_9H_{19}$	"	"	trans
108	"	"	"	cis
109	$n\text{-}C_{16}H_{33}$	"	"	trans
110	"	"	"	cis
111	$n\text{-}C_{18}H_{37}$	"	"	trans
112	"	"	"	cis
113	CH_3	CH_3	"	-
114	$n\text{-}C_9H_{19}$	H	$CH_2(CH_2)_2CH_2N(CH_3)_2$	m

- Cont'd -

115	$n\text{-}C_9H_{19}$	H	$CH_2CH_2N(C_2H_5)_2$	trans
116	"	"	"	cis
117	"	"	$CH_2CH_2\underset{H}{N}C_2H_5$	trans
118	"	"	"	cis
119	"	"		m
120	"	"		m
121	"	"	$CH_2CH_2NH_2$	m
122	"	"		m
123	$(CH_3)_2CH(CH_2)_3CHCH_3(CH_2)_2$	"	$CH_2CH_2N(CH_3)_2$	trans
124	$CH_2=CHCH_2$	"	"	trans
125		"	"	trans
126	$(CH_3)_2CH_2CH_2CH_2$	"	"	trans
127	CH_3	"	"	trans
128	"	"	"	cis

- Cont'd -

130			$-CH_2CH_2N(CH_3)_2$	-
131		H	"	trans
132	$CH_3(CH_2)_3O(CH_2)_2$	$CH_3(CH_2)_3O(CH_2)_2$	$-CH_2CH_2N(CH_3)_2$	-
133	$CH_3(CH_2)_3O(CH_2)_2$	H	$CH_2CH_2N(CH_3)_2$	trans
134	$CH_3(CH_2)_3O(CH_2)_2O(CH_2)_2$	$CH_3(CH_2)_3O(CH_2)_2O(CH_2)_2$	$-CH_2CH_2N(CH_3)_2$	-
135	$CH_3(CH_2)_3O(CH_2)_2O(CH_2)_2$	H	$-CH_2CH_2N(CH_3)_2$	trans
136	Hydrochloride of No. 135			
137	$CH_3CH_2O(CH_2)_3-$	H	$-CH_2CH_2N(CH_3)_2$	m
138	Hydrochloride of No. 137			
139	$CH_2=CH_2CH_2O(CH_2)_2-$	$CH_2=CH_2CH_2O(CH_2)_2-$	$-CH_2CH_2N(CH_3)_2$	
140	$CH_2=CH_2CH_2O(CH_2)_2$	H	$-CH_2CH_2N(CH_3)_2$	m
141	$HO(CH_2)_2O(CH_2)_2-$	H	$-CH_2CH_2N(CH_3)_2$	m
142	$(CH_3)_2CHCH_2O(CH_2)_2$	$(CH_3)_2CHCH_2O(CH_2)_2$	$-CH_2CH_2N(CH_3)_2$	-
143	$(CH_3)_2CHCH_2O(CH_2)_2$	H	$-CH_2CH_2N(CH_3)_2$	m

- Cont'd -

144	Hydrochloride of No. 143			
145	$(CH_3)_3CO(CH_2)_2-$	H	$-CH_2CH_2N(CH_3)_2$	m
146	$CH_3(CH_2)_2O(CH_2)_2O(CH_2)_2$	$CH_3(CH_2)_2O(CH_2)_2O(CH_2)_2$	$CH_2CH_2N(CH_3)_2$	-
147	$CH_3(CH_2)_2O(CH_2)_2O(CH_2)_2$	H	$CH_2CH_2N(CH_3)_2$	m
148	Hydrochloride of No. 147			
149	$(CH_3)_2CHCH_2O(CH_2)_2O(CH_2)_2$	$(CH_3)_2CHCH_2O(CH_2)_2O(CH_2)_2$	$CH_2CH_2N(CH_3)_2$	-
150	$(CH_3)_2CHCH_2O(CH_2)_2O(CH_2)_2$	H	$CH_2CH_2N(CH_3)_2$	trans
151	Hydrochloride of No. 150			
152	$(CH_3)_2CHO(CH_2)_2O(CH_2)_2$	H	$CH_2CH_2N(CH_3)_2$	m
153	$(CH_3)_2CHO(CH_2)_2$	$(CH_3)_2CHO(CH_2)_2$	$CH_2CH_2N(CH_3)_2$	-
154	$(CH_3)_2CHO(CH_2)_2$	H	$CH_2CH_2N(CH_3)_2$	m
155	$CH_3O(CH_2)_2O(CH_2)_2$	H	$CH_2CH_2N(CH_3)_2$	m
156	$(CH_3)_2CHO(CH_2)_2O(CH_2)_2$	H	$CH_2CH_2N(CH_3)_2$	trans
157	Hydrochloride of No. 156			

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158	$CH_3CH_2O(CH_2)_2O(CH_2)_2$	$CH_3CH_2O(CH_2)_2O(CH_2)_2$	$CH_2CH_2N(CH_3)_2$	
159	$CH_3CH_2O(CH_2)_2O(CH_2)_2$	H	$CH_2CH_2N(CH_3)_2$	m
160	Hydrochloride of No. 159			
161	$CH_3CH_2O(CH_2)_2O(CH_2)_2$	$CH_3CH_2O(CH_2)_2O(CH_2)_2$	$CH_2CH_2N(CH_3)_2$	-
162	$CH_3CH_2O(CH_2)_2O(CH_2)_2$	H	$CH_2CH_2N(CH_3)_2$	trans
163	Hydrochloride of No. 162			
164	$(CH_3)_3C(CH_2)_2SiO(CH_2)_2O(CH_2)_2$	$(CH_3)_3C(CH_2)_2SiO(CH_2)_2O(CH_2)_2$	$CH_2CH_2N(CH_3)_2$	-
165	$(CH_3)_3C(CH_2)_2Sio(CH_2)_2O(CH_2)_2$	H	$CH_2CH_2N(CH_3)_2$	m
166	$(CH_3)_3C(CH_2)_2SiO(CH_2)_2$	$(CH_3)_3C(CH_2)_2SiO(CH_2)_2$	$CH_2CH_2N(CH_3)_2$	
167	$(CH_3)_3C(CH_3)_2SiO(CH_2)_2$	H	$CH_2CH_2N(CH_3)_2$	m
168	$(CH_3)_3C(CH_3)_2SiO(CH_2)_3$	$(CH_3)_3C(CH_3)_2SiO(CH_2)_3$	$CH_2CH_2N(CH_3)_2$	m
169	$(CH_3)_3C(CH_3)_2SiO(CH_2)_3$	H	$CH_2CH_2N(CH_3)_2$	trans
170	$(CH_3)_2C(CH_3)_2SiO(CH_2)_3$	H	$CH_2CH_2N(CH_3)_2$	cis

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171	CF_3CH_2	H	$CH_2CH_2N(CH_3)_2$	m
172	$CF_3(CF)_2CH_2CH_2$	H	$CH_2CH_2N(CH_3)_2$	trans
174	Hydrochloride of No. 73			
175	Hydrochloride of No. 75			
176	Hydrochloride of No. 77			
177	Hydrochloride of No. 79			

Properties of compounds prepared are shown in the following table.

Compound No.	M.P. or NMR(δ, $CDCl_3$)[PPM]	a) IR($CHCl_3$)[cm^{-1}] b) IR(nujol)[cm^{-1}]
29	2.5-3.0(3H, m), 3.6-4.0(3H, m), 3.85(3H, s), 3.88(3H, s), 5.23(1H, d, J=1.5Hz)	a) 2940, 2845, 1675, 1595, 1440, 1360, 1020.
30	0.99-1.08(3H, m), 1.59-1.67(3H, m), 3.6-3.85(1H, m), 3.9-4.05(0.6H, m), 4.05-4.20(0.4H, m), 5.61(0.4H, d, J=1.7Hz), 5.63(0.6H, s).	a) 2930, 1670, 1585, 1575, 1445, 1419, 1120.
31	1.63(3H, d, J=7.1Hz), 3.0-3.2(1H, m), 4.0-4.2(1H, m), 4.4-4.6(1H, m), 5.0-5.3(2H, m), 5.57(1H, d, J=2Hz), 5.6-5.8(1H, m).	a) 1674, 1590, 1579, 1120.
32	46-48°C	b) 1650, 1595, 1580, 1275, 1180, 1021.
33	1.63(3H, d, J=7.1Hz), 3.26-3.34(1H, m), 4.06-4.12(1H, m), 4.61-4.70(1H, m), 5.80(1E, d, J=1.7Hz).	a) 3405, 1680, 1578, 1400, 1348.
34	1.67(3H, d, J=7.1Hz), 3.23-3.30(1H, m), 3.96-4.05(1H, m), 4.61-4.69(1H, m), 5.80(1H, s).	a) 3405, 1680, 1578, 1400, 1350.
35	111-111.5°C	b) 1660, 1580, 1418, 1305, 1149, 1025, 1005.

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36	107-107.5°C	b) 1664, 1649, 1579, 1420, 1305, 1157.
37	92-93°C	b) 1662, 1576, 1512, 1420, 1269, 1239, 1142, 1025.
38	92-94°C	b) 1658, 1585, 1511, 1416, 1260, 1140, 1021.
39	1.59-1.67(3H, m), 3.26(1.8H, s), 3.29(1.2H, s), 5.63(0.4H, d, J=1.7Hz), 5.65(0.6H, s).	a) 2920, 2860, 1760, 1572, 1440, 1300, 1111.
40	104-106°C	b) 1677, 1650, 1580, 1299, 1145, 1025, 710.
41	100-101°C	b) 1681, 1656, 1591, 1580, 1140.
42	1.0-2.4(5H, m), 2.73(1H, s), 2.74(1H, s), 3.9-4.2(1H, m), 5.48(0.7H, d, J=2.0Hz), 5.50(0.3H, s).	a) 2950, 1670, 1590, 1578, 1388, 1301, 1020.
43	0.9-2.4(7H, m), 2.72(1.2H, s), 2.75(1.8H, s), 3.9-4.1(1H, m), 5.47(0.6H, d, J=2.0Hz), 5.49(0.4H, s).	a) 2960, 2940, 1670, 1595, 1581, 1392, 1015.
44	0.9-2.4(8H, m), 2.72(3H, s), 4.1-4.3(1H, m).	a) 2955, 1672, 1590, 1579, 1305.

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45	0.8-2.5(8H, m), 5.47(0.5H, d, J=2.0Hz), 5.49(0.5H, s).	a) 2950, 1674, 1589, 1578.
46	0.8-2.3(11H, m), 2.72(0.3H, s), 2.74(2.7H, s), 3.9-4.1(1H, m), 5.47(0.9H, d, J=1.7Hz), 5.49(0.1H, s).	a) 2930, 2855, 1670, 1590, 1578, 1390, 1120, 1009.
47	0.8-2.3(13H, m), 2.72(0.6H, s), 2.74(2.4H, s), 3.9-4.1(1H, m), 5.47(0.8H, d, J=2.0Hz), 5.49(0.2H, s).	a) 2925, 2855, 1670. 1589, 1578, 1390, 1300, 1020.
48	0.8-2.4(19H, m), 2.72(1H, s), 2.74(2H, s), 3.9-4.1(1H, m), 5.47(0.74H, d, J=2.0Hz), 5.49(0.3H, s).	a) 2920, 2850, 1670, 1589, 1576, 1300, 1009.
49	52.5-53°C	b) 1663, 1578, 1420, 1020.
50	67.5-68.5°C	b) 1660, 1575, 1408, 1391, 1325, 1250, 708.
51	0.8-2.4(21H, m), 2.72(1H, s), 2.74(2H, s), 3.9-4.1(1H, m), 5.47(0.7H, d, J=2.0Hz), 5.49(0.3H, s).	a) 2920, 2850, 1670, 1590, 1578, 1300, 1010.
52	3.86(3H, s), 3.87(3H, s), 5.17(1H, d, J=1.7Hz).	a) 2930, 2860, 1670, 1590, 1360.
53	3.84(3H, s), 3.87(3H, s), 5.20(1H, s).	a) 2920, 2850, 1670, 1589, 1138, 1018.

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54	57-58°C	b) 1724, 1693, 1579, 1432, 1292, 1023, 715.
55	47-48°C	b) 1742, 1683, 1577, 1420, 1295, 1210, 1025, 709.
56	55-56°C	b) 1739, 1660, 1550, 1214.
57	46-47°C	b) 1740, 1667, 1657, 1582, 1191, 1020.
58	55-56°C	b) 1673, 1590, 1414, 1267, 1239, 1025, 800.
59	77-78°C	b) 1675, 1586, 1512, 1253, 1021.
60	2.71(3H, s), 4.01(0.85H, dd, J=3.5 and 11.3Hz), 4.05-4.2(0.15H, m), 5.4-5.5(1H, m).	b) 1665, 1585, 1570, 1310, 1265, 1025.
61	78-79°C	b) 1660, 1578, 1262, 1025, 735.
62	0.9-1.1(6H, m), 1.1-2.1(8H, m), 2.69(3H, s), 5.39(1H, s).	a) 2950, 2930, 1673, 1589, 1578, 1388, 901.

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63	2.72(0.75H, s), 2.75-(2.25H, s), 4.03-4.09(0.25H, m), 4.10-4.17(0.75H, m), 5.46(0.75H, d, J=2.0Hz), 5.50(0.25H, s).	a) 2900, 1675, 1590, 1580, 1390, 1350, 1300.
64	133-135°C	b) 3220, 1679, 1581, 1315, 1024, 721.
65	81.5-82.5°C	b) 2760, 1660, 1580, 1419, 1276, 1220, 1063, 847.
66	73-74°C	b) 1662, 1647, 1577, 1420, 1327, 1305, 1165, 1039, 1020.
67	0.98(3H, t, J=7.3Hz), 2.15(6H, s), 2.35-2.55(1H, m), 3.7-3.9(1H, m), 4.0-4.1(1H, m) 5.86(1H, d, J=1.7Hz)	a) 1670, 1578, 1355, 1010.
68	65-66°C	b) 1659, 1585, 1419, 1291, 1260, 1021.
69	0.94(3H, t, J=6.6Hz), 2.15(6H, s), 2.4-2.52(1H, m), 2.64-2.74(1H, m), 3.75-3.85(1H, m), 4.00-4.06(1H, m), 5.86(1H, d, J=2.0Hz)	a) 2930, 2790, 1665, 1580, 1360, 1098.
70	0.92(3H, t, J=7.0Hz), 2.13(6H, s), 2.37-2.54(1H, m), 2.64-2.74(1H, m), 3.75-3.85(1H, m), 3.95-4.0(1H, m), 5.85(1H, s)	a) 2920, 2780, 1665, 1579, 1357, 1096.

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71	0.90(3H, t, J=7.0Hz), 2.15(6H, s), 2.39-2.51(1H, m), 2.64-2.74(1H, m), 3.75-3.85(1H, m), 4.0-4.06(1H, m), 5.86(1H, d, J=2.0Hz)	a) 2920, 2770, 1662, 1577, 1358.
72	0.89(3H, t, J=7.0Hz), 2.13(6H, s), 2.38-2.54(1H, m), 2.64-2.74(1H, m), 3.75-3.85(1H, m), 3.95-4.00(1H, m), 5.84(1H, s)	a) 2920, 2770, 1662, 1577, 1358.
73	0.89(3H, t, J=6.7Hz), 2.15(6H, s), 2.35-2.55(1H, m), 2.6-2.8(1H, m), 3.7-3.9(1H, m), 4.0-4.1(1H, m), 5.86(1H, d, J=2.0Hz)	a) 2930, 1664, 1578, 1358, 1295.
74	0.88(3H, t, J=6.7Hz), 2.13(6H, s), 2.35-2.55(1H, m), 2.6-2.8(1H, m), 3.7-3.9(1H, m), 3.9-4.05(1H, m), 5.84(1H, s)	a) 2920, 1660, 1578, 1359, 1296, 1097.
75	0.88(3H, t, J=6.7Hz), 2.15(6H, s), 2.35-2.55(1H, m), 2.6-2.8(1H, m), 3.75-3.90(1H, m), 4.0-4.1(1H, m), 5.86(1H, d, J=1.7Hz)	a) 2930, 1665, 1580, 1410, 1355, 1295, 1020.
76	0.88(3H, t, J=6.8Hz), 2.13(6H, s), 2.35-2.55(1H, m), 2.6-2.8(1H, m), 3.75-3.85(1H, m), 3.9-4.0(1H, m), 5.84(1H, s)	a) 2915, 2860, 1665, 1575, 1355, 1290, 1093.

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77	0.88(3H, t, J=6.7Hz), 2.16(6H, s), 2.40-2.55(1H, m), 2.60-2.75(1H, m), 3.75-3.85(1H, m), 4.0-4.05(1H, m), 5.85(1H, d, J=2.0Hz)	a) 2920, 2855, 1670, 1577, 1358, 1295.
78	0.87(3H, t, J=6.7Hz), 2.15(6H, s), 2.35-2.55(1H, m), 2.6-2.8(1H, m), 3.75-3.85(1H, m), 3.9-4.0(1H, m), 5.84(1H, s)	a) 2920, 2855, 1670, 1578, 1355.
79	0.88(3H, t, J=6.7Hz), 2.16(6H, s), 2.40-2.52(1H, m), 2.60-2.75(1H, m), 3.75-3.85(1H, m), 4.0-4.05(1H, m), 5.85(1H, d, J=1.7Hz)	a) 2920, 2855, 1655, 1577, 1350.
80	0.88(3H, t, J=6.6Hz), 2.16(6H, s), 2.39-2.50(1H, m), 2.64-2.75(1H, m), 3.76-3.85(1H, m), 3.95-4.00(1H, m), 5.84(1H, s)	a) 2920, 2850, 1665, 1576, 1355, 1290.
81	0.88(3H, t, J=6.6Hz), 2.16(6H, s), 2.40-2.52(1H, m), 2.63-2.74(1H, m), 3.75-3.85(1H, m), 4.0-4.05(1H, m), 5.85(1H, d, J=2.0Hz)	a) 2920, 2860, 1663, 1577, 1356, 1290, 1090.
82	0.88(3H, t, J=6.8Hz), 2.14(6H, s), 2.39-2.49(1H, m), 2.63-2.74(1H, m), 3.75-3.85(1H, m), 3.95-4.00(1H, m), 5.84(1H, s)	a) 2915, 2855, 1670, 1575, 1358, 1295, 1092.

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83	0.88(3H, t, J=6.7Hz), 2.16(6H, s), 2.40-2.52(1H, m), 2.63-2.75(1H, m), 3.75-3.85(1H, m), 4.00-4.05(1H, m), 5.85(1H, d, J=2.0Hz)	a) 2910, 2855, 1660, 1579, 1355, 1295, 1095.
84	0.88(3H, t, J=6.6Hz), 2.14(6H, s), 2.39-2.49(1H, m), 2.63-2.74(1H, m), 3.75-3.85(1H, m), 3.95-4.00(1H, m), 5.84(1H, s)	a) 2920, 2850, 1670, 1575, 1355, 1290.
85	35.5-36.5°C	b) 1683, 1290, 1017, 705.
86	71.5-72.5°C	b) 1654, 1577, 1420, 1268, 712.
87	40-41°C	b) 1685, 1573, 1415, 1298, 1155, 710.
88	59-60°C	b) 1653, 1575, 1420, 1265, 1145, 710.
89	45-46°C	b) 1685, 1577, 1298, 1260, 1154, 710.
90	76.5-77.5°C	b) 1652, 1573, 1418, 1300, 712.
91	42-44°C	b) 1687, 1672, 1300, 1021.

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92	65-66°C	b) 1650, 1577, 1142, 1020,
93	52.5-53.5°C	b) 1685, 1578, 1295, 1259.
94	81-82°C	b) 1652, 1577, 1420, 1142, 713.
95	68-70°C	b) 1690, 1578, 1300, 1260, 1159, 1020.
96	63-64°C	b) 1655, 1579, 1421, 1270, 1144, 713.
97	57.5-58.5°C	b) 1690, 1575, 1300, 1023, 710.
98	84.5-85.5°C	b) 1652, 1575, 1419, 1301, 1262, 1140, 709.
99	53-56°C	b) 1684, 1572, 1410, 709.
100	73.5-75°C	b) 1653, 1578, 1420, 1265, 1220, 710.
101	4.07(1H, dq, J=1.7 and 7.0Hz), 5.65(1H, d, J=1.7Hz)	a) 2925, 2810, 1670, 1573, 1445, 1113.

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102	3.96(1H, dq, J=7.0Hz), 5.66(1H, s)	a) 2920, 2805, 1665, 1572, 1445, 1110.
103	0.97(3H, t, J=7.3Hz), 2.16(6H, s), 3.6-3.75(1H, m), 4.0-4.1(1H, m), 5.63(1H, d, J=2.0Hz)	a) 2900, 1663, 1575.
104	0.97(3H, t, J=7.3Hz), 2.22(6H, s), 3.55-3.70(1H, m), 3.9-4.0(1H, m), 5.68(1H, s).	a) 2860, 1660, 1410, 1300.
105	0.89(3H, t, J=6.6Hz), 2.21(6H, s), 3.6-3.75(1H, m), 4.0-4.1(1H, m), 5.63(1H, d, J=2.0Hz)	a) 2910, 2860, 1665.
106	0.88(3H, t, J=6.6Hz), 2.13(6H, s), 3.55-3.70(1H, m), 3.9-4.0(1H, m), 5.65(1H, S).	a) 2900, 2870, 1660, 1579.
107	2.15(6H, s), 4.0-4.07(1H, m), 5.63(1H, d, J=1.7Hz)	a) 2910, 2855, 1670, 1577, 1300, 1020.
108	2.13(6H, s), 3.94(1H, dd, J=3.7 and 9Hz), 5.65(1H, s)	a) 2930, 2860, 1670, 1580, 1300, 1020.
109	77°C-78°C	b) 1675, 1586, 1512, 1253, 1021.
110	55-56°C	b) 1673, 1590, 1414, 1267, 1239, 1025, 800.

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111	63-64°C	b) 1655, 1576, 1421, 1269, 719.
112	73-74°C	b) 1652, 1581, 1424, 1310, 1028, 715.
113	65.5-66.5°C	b) 1659, 1585, 1400, 1302, 1269, 1200, 1129, 703.
114	0.85-0.9(3H, m), 2.16(4H, S), 2.17(2H, s), 3.0-3.75(1H, m), 3.9-4.0(0.67H, m), 4.0-4.1(0.33H, m), 5.59(0.33H, d, J=2.0Hz), 5.62(0.67H, S)	a) 2840, 1655, 1408, 1350.
115	0.88(3H, t, J=6.7Hz), 0.97(6H, t, J=7.1Hz), 3.65-3.8(1H, m), 3.95-4.05(1H, m), 5.89(1H, d, J=2.0Hz)	a) 2850, 1660.
116	0.87(3H, t, J=6.7Hz), 0.95(6H, t, J=7.1Hz), 3.6-3.75(1H, m), 3.9-4.0(1H, m), 5.90(1H, m)	a) 2880, 1658.
117	0.88(3H, t, J=6.6Hz), 1.06(3H, t, J=7.1Hz), 3.7-3.9(1H, m), 4.0-4.1(1H, m), 5.79(1H, d, J=1.7Hz)	a) 2860, 1665.
118	0.88(3H, t, J=6.7Hz), 1.05(3H, t, J=7.1Hz), 3.65-3.80(1H, m), 3.95-4.0(1H, m), 5.81(1H, s)	a) 2900, 2850, 1663.

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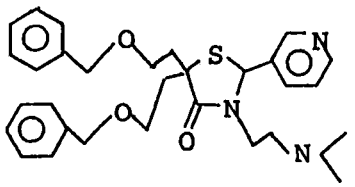
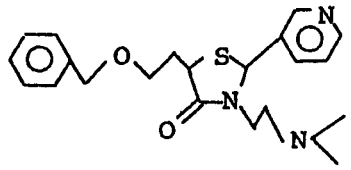
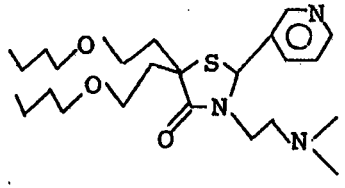
119	0.85-0.9(3H, m), 2.6-2.8(2H, m), 3.75-4.1(2H, m), 5.88-5.86(1H, m)	a) 2850, 1658, 1350.
120	2.83-2.88(4H, m), 3.66-3.78(4H, m), 3.94-3.99(0.5H, m), 3.99-4.03(0.5H, m) 5.85(0.5H, d, J=1.9Hz), 5.86(0.5H, s)	a) 2850, 1660.
121	3.63-3.76(2H, m), 3.96-4.01(0.5H, m), 4.01-4.08(0.5H, m), 5.73(0.5H, d, J=1.7Hz), 5.76(0.5H, s)	a) 2850, 1660, 1577, 1403.
122	2.17(3H, s), 5.90(0.5H, d, J=1.7Hz), 5.91 (0.5H, s)	a) 2855, 1670, 1630.
123	0.87(6H, d, J=6.6Hz), 0.95(3H, d, J=6.4Hz), 2.15(6H, s), 3.75-3.85(1H, m), 3.99-4.05(1H, m), 5.86(1H, d, J=2.0Hz)	a) 2855, 1660, 1578, 1358.
124	2.15(6H, s), 3.75-3.85(1H, m), 4.0-4.05(1H, m), 5.14-5.26(2H, m) 5.85(1H, d, J=2.0Hz), 5.8-6.0(1H, m)	a) 2870, 1660, 1578, 1403, 1352.
125	3.11-3.44(2H, m), 3.67-3.76(1H, m), 4.03-4.35(1H, m), 5.49(1H, d, J=2.0Hz)	a) 2770, 1660, 1577.
126	2.15(6H, s), 3.75-3.85(1H, m), 4.0-4.05(1H, m), 5.86(1H, d, J=1.7Hz)	a) 2870, 1655, 1578, 1405, 1353.
127	1.61(3H, d, J=6.8Hz), 2.16(6H, s) 3.8-3.9(1H, m), 3.95-4.15(1H, m) 5.88(1H, d, J=1.7Hz)	a) 2930, 1690, 1580, 1359, 1149.
128	71.5-72.5°C	b) 1659, 1573, 1415, 1283,1100.

Compound No.		M.P. or NMR (δ ppm)	IR cm^{-1}
130		$CDCl_3$; 2.03(6H, s), 4.45-4.6(4H, m), 5.64(1H, s)	$CHCl_3$; 2860, 1665, 1579, 1090
131	 trans	$CDCl_3$; 2.12(6H, S), 4.52(2H, S), 5.80(1H, d, J=2.0Hz)	$CHCl_3$; 1665, 1590, 1405, 1090
132		$CDCl_3$; 2.13(6H, S), 3.3-4.5(4H, m), 3.55-3.8(5H, m), 5.72(1H, S)	$CHCl_3$; 2870, 1665, 1579, 1095

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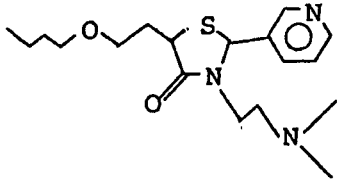
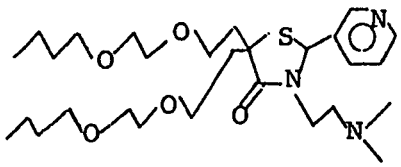
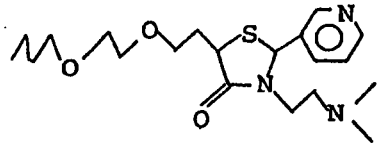
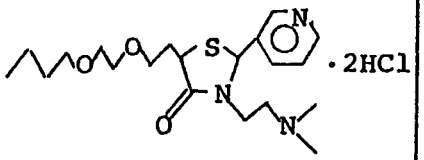
133	 trans	$CDCl_3$; 2.15(6H, S), 4.1-4.2(1H, m), 5.83(1H, d, J=1.7Hz)	$CHCl_3$; 2850, 1662, 1578, 1100
134		$CDCl_3$; 0.86-0.95(6H, m), 1.30-1.63(8H, m), 2.13(6H, S), 5.73(1H, S)	$CHCl_3$; 2940, 2880, 1672, 1356, 1100
135	 trans	$CDCl_3$; 2.15(6H, S), 4.12-4.17(1H, m), 5.83(1H, d, J=1.7Hz)	$CHCl_3$; 2860, 1662, 1572, 1350, 1095
136	 .2HCl mix	DMSO; 0.85(3H, t, J=7.3Hz), 4.21-4.34(1H, m), 6.09(0.7H, d, J=1.5Hz), 6.13(0.3H, S)	KBr; 2870, 2680, 1678, 1418, 1110

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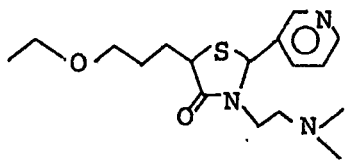
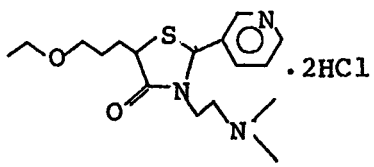
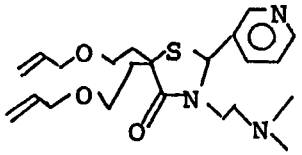
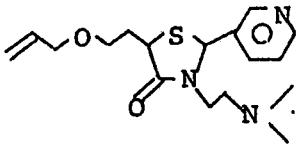
137	 mix	$CDCl_3$; 2.14(1.8H, S), 2.15(1.2H, S), 4.01-4.08(1H, m), 5.85(1H, d, J=2Hz)	$CHCl_3$; 2940, 2860, 1670, 1598, 1590, 1380, 1360, 1300, 1105
138	 .2HCl mix	m.p. 75-78°C	KBr; 2930, 2870, 2700, 1675, 1414, 1108
139		$CDCl_3$; 2.12(6H, S), 5.12-5.33(4H, m), 5.72(1H, S), 5.85-6.00(2H, m)	$CHCl_3$; 1680, 1605, 1585, 1355, 1100, 990
140	 mix	$CDCl_3$; 2.13(1.2H, S), 2.15(4.8H, S), 4.13-4.18(1H, m), 5.16-5.32(2H, m), 5.79-5.82(2H, m)	$CHCl_3$; 1680, 1595, 1580, 1350, 1100

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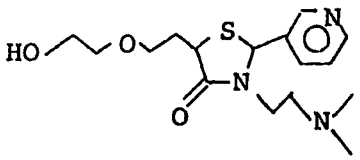
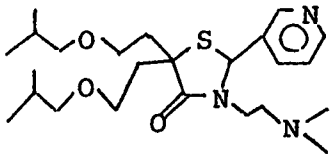
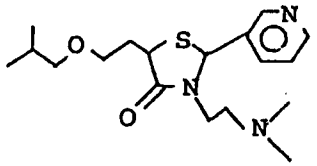
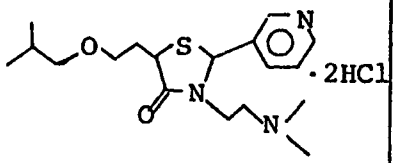
141		$CDCl_3$; 2.13(3H, S), 2.15(3H, S), 4.09-4.19(1H, m), 5.85(0.5H, S), 5.88(0.5H, d, J=2Hz)	$CHCl_3$; 3300-3500 (br), 2825, 2775, 1670, 1597, 1590, 1360, 1290
142		$CDCl_3$; 0.92-0.87(12H, m), 2.13(6H, S), 5.73(1H, S)	$CHCl_3$; 2870, 1675, 1595, 1580, 1100
143	 mix	$CDCl_3$; 0.89(6H, d, J=6.6Hz), 2.13(2.1H, S), 2.15(3.6H, S), 4.09-4.16(1H, m), 5.83(0.6H, d, J=2Hz), 5.84(0.4H, S)	$CHCl_3$; 2870, 1670, 1590, 1580, 1360, 1100
144	 ·2HCl mix	DMSO; 0.84(6H, d, J=6.8Hz), 4.31-4.34(1H, m), 6.09(0.8H, d, J=1.5Hz), 6.12(0.2H, S)	KBr; 2960, 2870, 2690, 1675, 1420, 1120

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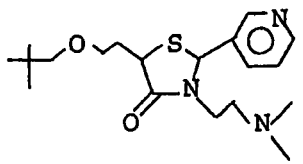
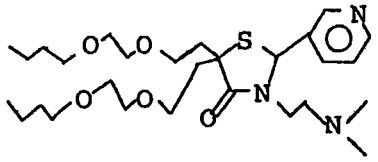
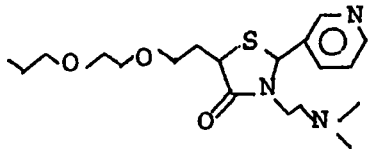
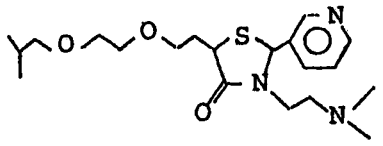
145	 mix	$CDCl_3$; 1.17(9H, S), 2.14(3H, S), 2.15(3H, S), 4.07-4.15(1H, m), 5.82(1H, m)	$CHCl_3$; 2930, 2820, 2775, 1670, 1590, 1580, 1360, 1300, 1095
146		$CDCl_3$; 0.87-0.95(6H, m), 2.12(6H, S), 3.19-3.24(4H, m), 5.74(1H, S)	$CHCl_3$; 2940, 2875, 1672, 1358, 1104
147	 mix	$CDCl_3$; 0.90(3H, t, J=7Hz), 2.14(3H, S), 2.15(3H, S), 4.08-4.17(1H, m), 5.83-5.84(1H, m)	$CHCl_3$; 2925, 2870, 2825, 2775, 1670, 1590, 1580, 1360, 1300, 1100
148	 mix	$DMSO-d_6$; 0.83(3H, t, J=7.5Hz), 4.31-4.34(1H, m), 6.09(0.8H, d, J=1.5Hz), 6.12(0.2H, S)	KBr; 2875, 2690, 1678, 1408, 1114

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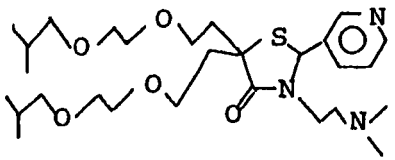
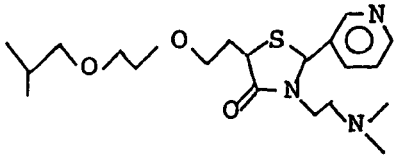
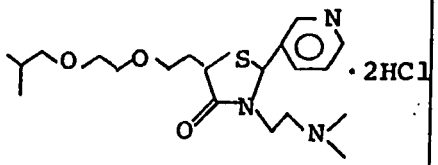
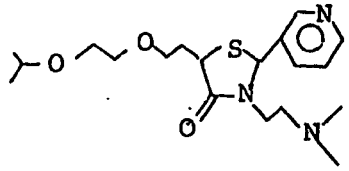
149		$CDCl_3$; 0.86-0.92(12H, m), 1.2(6H, S), 3.19-3.24(4H, m), 5.74(1H, S)	$CHCl_3$; 2950, 2880, 1672, 1356, 1104
150	 trans	$CDCl_3$; 0.88(6H, d, J=6.6Hz), 2.14(6H, S), 3.21(2H, d, J=6.8Hz), 4.13-4.16(1H, m), 5.83(1H, d, J=1.7Hz)	$CHCl_3$; 2940, 2863, 2775, 1668, 1592, 1578, 1358, 1096
151	 mix	DMSO-d_6; 0.82(6H, d, J=6.6Hz), 4.30-4.33(1H, m), 6.11(0.8H, d, J=1.5Hz), 6.14(0.2H, S)	KBr; 2960, 2870, 2700, 1680, 1470, 1118
152	 mix	$CDCl_3$; 1.15(6H, d, J=6Hz), 2.13(3H, S), 2.15(3H, S), 4.08-4.16(1H, m), 5.83-5.84(1H, m)	$CHCl_3$; 2870, 2825, 2775, 1670, 1590, 1580, 1125

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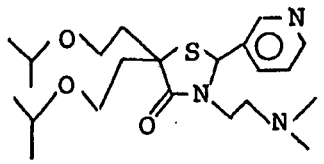
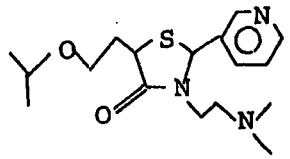
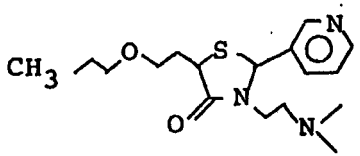
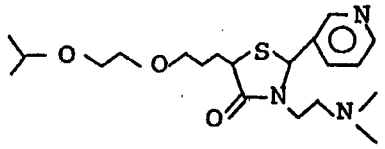
153		$CDCl_3$; 1.12-1.72(12H, m), 3.54-3.78(7H, m), 5.72(1H, S)	$CHCl_3$; 2870, 2825, 2775, 1670, 1595, 1580, 1385, 1370, 1125, 1070
154	 mix	$CDCl_3$; 1.13-1.59(1H, m), 3.74-3.86(1H, m), 4.07-4.16(1H, m), 5.83(1H, m)	$CHCl_3$; 2935, 2825, 2775, 1670, 1590, 1580, 1125
155	 mix	$CDCl_3$; 2.13(3H, S), 2.15(3H, S), 3.38(3H, S), 4.08-4.13(1H, S), 5.34(1H, D, J=2Hz)	$CHCl_3$; 1670, 1590, 1580, 1355, 1090
156	 trans	$CDCl_3$; 1.16(6H, d, J=6.1Hz), 2.15(6H, S), 4.05-4.08(1H, m), 5.35(1H, d, J=2Hz)	$CHCl_3$; 2870, 2825, 2780, 1670, 1595, 1580, 1370, 1120

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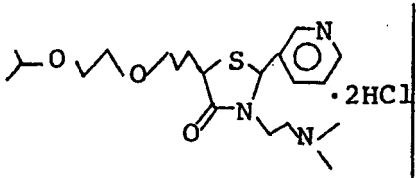
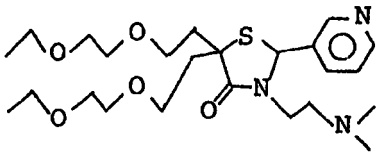
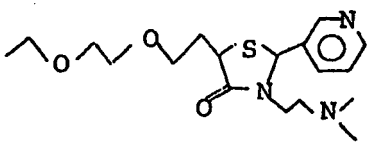
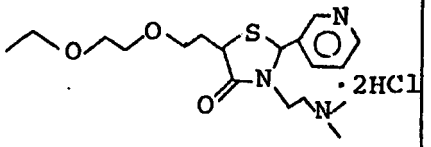
157	 ·2HCl trans	DMSO-d_6; 1.07(6H, d, J=6.1Hz), 4.33-4.36(1H, m), 6.12(1H, d, J=1.4Hz)	KBr; 2980, 2700, 1682, 1475, 1385, 1122 (KBr)
158		$CDCl_3$; 1.19-1.25(6H, m), 2.14(6H, S), 5.77(1H, S)	$CHCl_3$; 2875, 1670, 1350, 1104
159	 mix	$CDCl_3$; 1.20(3H, t, J=7Hz), 2.13(1H, S), 2.15(5H, S), 4.13-4.16(1H, m), 5.84(1H, d, J=2Hz)	$CHCl_3$; 2870, 2825, 2780, 1670, 1600, 1585, 1330, 1102
160	 ·2HCl mix	DMSO-d_6; 1.08(3H, t, J=7Hz), 4.31-4.34(1H, m), 6.01(0.8H, d, J=1.5Hz), 6.12(0.2H, S)	KBr; 2880, 2690, 1425, 1115

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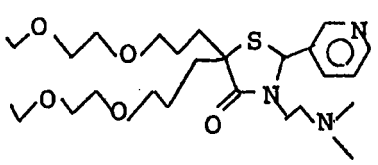
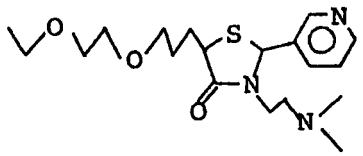
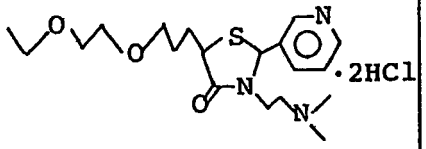
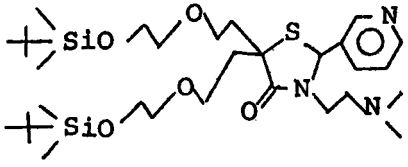
161		$CDCl_3$; 1.19-1.25(6H, m), 2.13(6H, S), 5.77,(1H, S)	$CHCl_3$; 2870, 1666, 1348, 1100
162	 trans	$CDCl_3$; 1.22(3H, t, J=7.1Hz), 2.15(6H, S), 4.05-4.07(1H, m), 5.85(1H, d, J=1.7Hz)	$CHCl_3$; 2865, 2820, 2775, 1670, 1593, 1580, 1353, 1100
163	 trans	DMSO-d_6; 1.10(3H, t, J=7.1Hz), 4.33-4.37(1H, m), 6.12(1H, d, J=1.1Hz)	KBr; 2875, 2680, 1680, 1110
164		$CDCl_3$; 0.05(6H, S), 0.08(6H, S), 0.88(9H, S), 0.90(9H, S), 2.15(6H, S), 5.72(1H, S)	$CHCl_3$; 2925, 2800, 1675, 1590, 1580, 1460, 1360, 1100, 830

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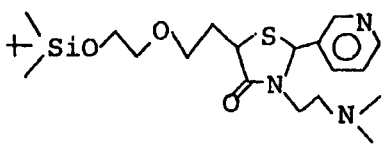
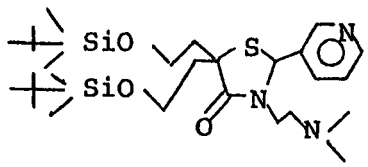
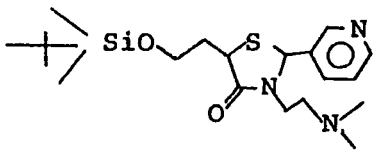
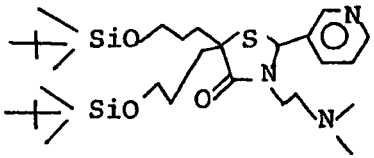
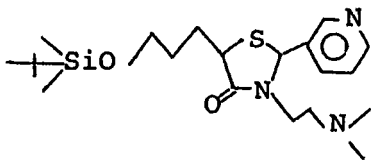
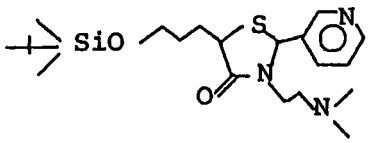
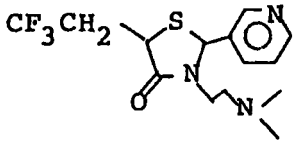
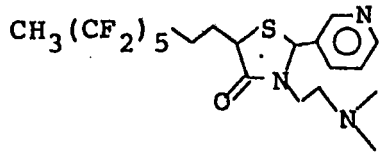
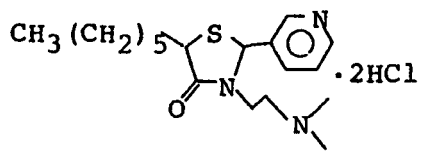
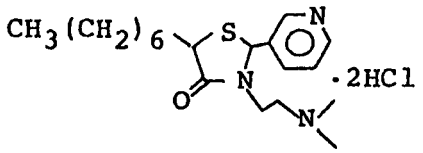
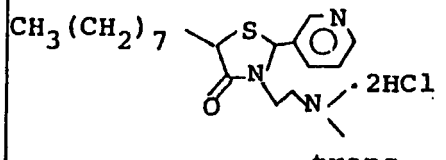
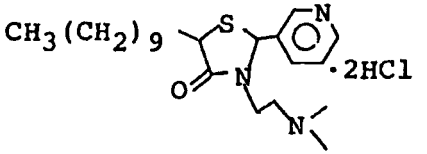
165	 mix	$CDCl_3$; 0.05(6H, S), 0.88(7H, S), 2.14(2.4H, S), 2.15(3.6H, S), 4.09-4.16(1H, m), 5.83(0.6H, d, J=1.7Hz), 5.85(0.4H, S)	$CHCl_3$; 2925, 2860, 1675, 1590, 1580, 1360, 1095
166		$CDCl_3$; 0.05-0.07(12H, m), 0.88(9H, S), 0.90(9H, S), 2.13(6H, S), 5.73(1H, S)	$CHCl_3$; 2925, 2860, 1670, 1600, 1460, 1360, 1090, 830
167		$CDCl_3$; 0.05(6H, S), 0.89(9H, S) 2.14(2.4H, S), 2.15(3.6H, S), 4.08-4.16(1H, m), 5.83(0.6H, d, J=2Hz), 5.85(0.4H, S)	$CHCl_3$; 2925, 2860, 2825, 2780, 1670, 1590, 1580, 1460, 1360, 1100, 830
168		$CDCl_3$; 0.04-0.07(12H, m), 0.88(9H, S), 0.90(9H, S), 2.13(6H, S), 5.81(1H, S)	$CHCl_3$; 2925, 2850, 2770, 1670, 1600, 1590, 1360, 1090, 830

- Cont'd -

169	 trans	$CDCl_3$; 0.06(6H, S), 0.81(9H, S), 2.15(6H, S), 3.67(2H, t, J=6Hz), 4.06-4.10(1H, m), 5.86(1H, d, J=2Hz)	$CHCl_3$; 1660, 1355, 1090, 830
170	 cis	m.p. 65.5-66°C	nujol; 1660, 1090, 850, 775
171	 mix	$CDCl_3$; 2.13(3H, S), 2.16(3H, S), 2.63(1H, S), 2.67(1H, S), 4.15-4.26(1H, m), 5.85-5.91(1H, m)	$CHCl_3$; 1680, 1380, 1300, 1140
172	 trans	m.p. 98.5-99.5°C	nujol; 1670, 1590, 1580, 1140, 985

- Cont'd -

174	 trans	89 - 92°C	KBr; 2920, 2850, 2680, 1676, 1462
175	 trans	130-131.5°C	KBr; 2930, 2860, 2680, 1680, 1470
176	 trans	157-160°C	KBr; 2925, 2860, 2670, 1680, 1464
177	 trans	175-177°C	KBr; 2925, 2850, 2670, 1678, 1466

Example 29

Preparation of (+)-cis-3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 178)

A solution of N-nicotinylidenemethylamin (4.37 g, 36 mmol) in tetrahydr furan (20 ml) was added dropwise to a solution of (-)-2-mercaptopropionic acid (3.86 g, 36 mmol) in tetrahydrofuran (40 ml) with stirring under a stream of nitrogen while cooling with ice. The reaction was allowed to proceed for 12 hours.

Then, the product mixture was dissolved in ethyl acetate (50 ml) and the solution was washed in turn with saturated aqueous $NaHCO_3$ (20 ml), water (20 ml), and aqueous NaCl, and dried. The solvent was removed under reduced pressure, giving a crude product in crystalline form (6.97 g), which was then washed with ether (10 ml) at 0 to 5°C and, upon recrystallization from ether (10 ml) at -10°C, gave (+)-cis-3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one (3.77 g, 50% yield).

m.p. 66.5-68.5°C

$[\alpha]_D^{26}$ = +20.5° (C 0.44, $CHCl_3$)

Example 30

Preparation of (-)-cis-3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 179)

According to the procedure of Example 29, the title compound (3.24 g, 52% yield) was prepared from (+)-2-mercaptopropionic acid (3.19 g, 30 mmol) and N-nicotinylidenemethylamine (3.61 g, 30 mmol).

m.p. 66.0-68.5°C

$[\alpha]_D^{25}$ = -21.3° (C 3.28, $CHCl_3$)

Example 31

Preparation of (-)-trans-3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 180)

Titanium tetraisopropoxide (1.42 g, 5.0 mmol) was added to a solution of (-)-2-mercaptopropionic acid (0.53 g, 5.0 mmol) in dichloromethane (5 ml) with stirring at room temperature under a stream of nitrogen. Then, a solution of N-nicotinylidenemethylamine (0.60 g, 5.0 mmol) in dichloromethane (2 ml) was similarly added dropwise at room temperature. The reaction was allowed to proceed for 5 hours. The product mixture, after addition of water, was celite-filtered using dichloromethane (20 ml) as washing liquid. The resulting organic layer was washed with water (10 ml) and then with aqueous NaCl, and dried. The solvent was removed under reduced pressure, leaving a crude product (0.44 g). Purification thereof by silica gel flash chromatography (hexane : 2-propanol = 4 : 1) gave (-)-trans-3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one (54 mg) in oily form.

n_D^{27} = 1.6043

$[\alpha]_D^{25}$ = -132.5° (C 0.28, $CHCl_3$)

Example 32

Preparation of (+)-trans-3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 181)

According to the procedure of Example 31, the title compound (49 mg) in oily form was prepared from (+)-2-mercaptopropionic acid (0.53 g, 5.0 mmol), titanium tetraisopropoxide (1.42 g, 5.0 mmol), and N-nicotinylidenemethylamine (0.60 g, 5.0 mmol).

n_D^{28} = 1.6039

$[\alpha]_D^{25}$ = +130.8° (C 0.34, $CHCl_3$)

Example 33

Preparation of 3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one hydrochloride (compound No. 182)

Conc. aqueous HCl (4.75 g, 45.6 mmol) was added dropwise to a solution of cis-3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one (10 g, 48 mmol) from Example 2 in ethanol (50 ml) at room temperature. Then the mixture was cooled to 0°C, and the precipitated crystals were filtered and the title compound (9.621 g, 86.2% yield) was obtained.

m.p. 190-193°C

Example 34

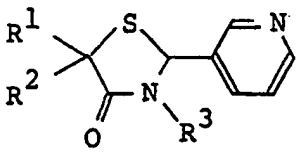
Preparation of half fumaric acid addition salt of 3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one (compound No. 183)

cis-3,5-Dimethyl-2-(3-pyridyl)thiazolidin-4-one (20 g, 96 mmol) from Example 2 and fumaric acid (5.58 g, 48 mmol) w r dissolved in ethanol (100 ml) and the solution was stirred for 1 hour at room temperature. Then the ethanol was rem ved under reduced pr ssure. The residue, upon recrystallizati n from thyl acetate, gave the titl compound (15.88 g, 62% yield).

m.p. 140-143°C

Claims

1. Thiazolidin-4-one derivatives represented by the following general formula [I] and acid addition salts thereof;



[I]

wherein;

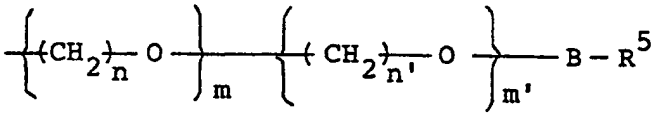
R^1 and R^2 are the same or different and denote each

(i) a residue represented by the general formula

-A-R^4

wherein, A denotes a single bond, C_1-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene and R^4 denotes hydrogen, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl, or C_1-C_8 haloalkyl, or

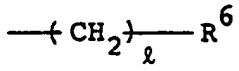
(ii) a residue represented by the general formula



wherein, B denotes a single bond or C_1-C_8 alkylene, R^5 denotes hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl, substituted silyl, or substituted or unsubstituted aryl, n and n' denote each an integer of 2 to 4, m denotes an integer of 1 to 3, and m' denotes an integer of 0 to 2; and

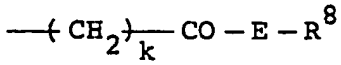
R^3 denotes hydrogen, C_1-C_2 alkyl, allyl, 2-propynyl, or a residue represented by

(a) the general formula



wherein, R^6 denotes halogen, an aryl group substituted or unsubstituted by one or more hydroxy or C_1-C_4 alkoxy groups, or a residue represented by the general formula -D-R^7 (D denotes oxygen or sulfur and R^7 denotes hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkanoyl) and ℓ denotes an integer of 2 to 4,

(b) the general formula

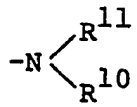


wherein, E denotes oxygen, sulfur, imino, or C_1-C_4 alkylimino, R^8 denotes hydrogen or C_1-C_4 alkyl, or -(E-R^8) denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms, and k denotes an integer of 1 to 3, or

(c) the general formula

-F-R^9

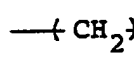
wherein, F denotes C_2-C_6 alkylene and R^9 denotes a nitrogen-containing heterocyclic aromatic residue or an amino group represented by the general formula



(R^{10} denotes hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkanoyl and R^{11} denotes hydrogen or C_1-C_4 alkyl or R^{10} in combination with R^{11} denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms),

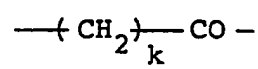
with the proviso that, when R^1 is hydrogen and R^2 is methyl, R^3 denotes hydrogen, C_1-C_2 alkyl, 2-propynyl, or a residue represented by

(a) the general formula



wherein, R^6 denotes halogen, an aryl group substituted or unsubstituted by one or more hydroxy or C_1-C_4 alkoxy groups, or a residue represented by the general formula -D-R^7 (D denotes oxygen or sulfur and R^7 denotes hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkanoyl) and ℓ denotes an integer of 2 to 4,

(b) the general formula

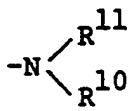


wherein, E denotes oxygen, sulfur, imino, or C_1-C_4 alkylimino, R^8 denotes hydrogen or C_1-C_4 alkyl, or -(E-R^8) denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms, and k denotes an integer of 1 to 3, or

(c) the general formula

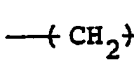
- F-R^9

wherein, F denotes C_2-C_6 alkylene and R^9 denotes a nitrogen-containing heterocyclic aromatic residue or an amino group represented by the general formula

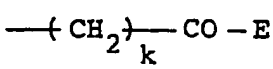


(R^{10} denotes hydrogen, C_2-C_4 alkyl, or C_1-C_4 alkanoyl and R^{11} denotes hydrogen or C_1-C_4 alkyl or R^{10} in combination with R^{11} denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms).

2. Compounds according to Claim 1, wherein R^3 is hydrogen, C_1-C_2 alkyl, allyl, 2-propynyl, or a residue represented by either the general formula



wherein R^8 and ℓ are as defined above or the general formula



wherein, E, R^8 and k are as defined above.

3. Compounds according to Claim 2, wherein R^1 and R^2 are residues represented by the general formula

-A-R^4

wherein A denotes C_1-C_4 alkylene and R^4 is as defined above.

4. Compounds according to Claim 2, wherein each of R^1 and R^2 is hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_3-C_8 cycloalkyl (C_1-C_4) alkyl, or aryl (C_2-C_4) alkyl.

5. Compounds according to Claim 1, wherein each of R^1 and R^2 is hydrogen or C_1-C_4 alkyl and R^3 is C_1-C_2 alkyl.

6. Compounds according to Claim 1, wherein R^3 is a residue represented by the general formula

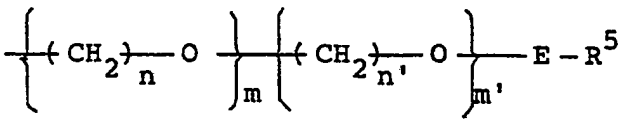
-F-R^9

wherein F and R^9 are as defined above.

7. Compounds according to Claim 6, wherein R^1 and R^2 are the same or different and denote each a residue represented by either the general formula

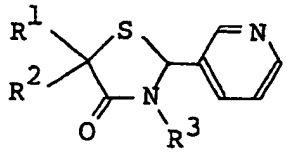
-A-R^4

wherein, A denotes a single bond or C_1-C_4 alkylene and R^4 denotes hydrogen, C_1-C_4 alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl, or C_1-C_6 haloalkyl or the general formula



wherein B, R^5, n, n', m, and m' are as defined above.

8. A pharmaceutical compositi n for treatment of the disease caused by the platelet activating factor, which comprises as an active ingredient a pharmaceutically effective amount of at least one compound r presented by the g neral formula



wherein;

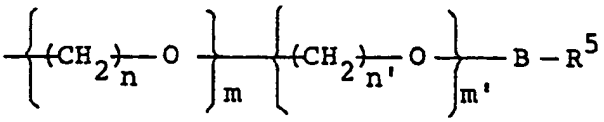
R^1 and R^2 are the same or different and denote each

(i) a residue represented by the general formula

-A-R^4

wherein, A denotes a single bond, C_1-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene and R^4 denotes hydrogen, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl, or C_1-C_6 haloalkyl, or

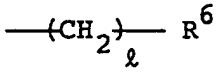
(ii) a residue represented by the general formula



wherein, B denotes a single bond or C_1-C_6 alkylene, R^5 denotes hydrogen, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl, substituted silyl, or substituted or unsubstituted aryl, n and n' denote each an integer of 2 to 4, m denotes an integer of 1 to 3, and m' denotes an integer of 0 to 2; and

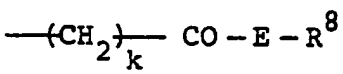
R^3 denotes hydrogen, C_1-C_2 alkyl, allyl, 2-propynyl, or a residue represented by

(a) the general formula



wherein, R^6 denotes halogen, an aryl group substituted or unsubstituted by one or more hydroxy or C_1-C_4 alkoxy groups, or a residue represented by the general formula -D-R^7 (D denotes oxygen or sulfur and R^7 denotes hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkanoyl) and ℓ denotes an integer of 2 to 4,

(b) the general formula

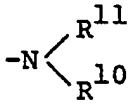


wherein, E denotes oxygen, sulfur, imino, or C_1-C_4 alkylimino, denotes hydrogen or C_1-C_4 alkyl, or -(E-R^8) denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms, and k denotes an integer of 1 to 3, or

(c) the general formula

-F-R^9

wherein, F denotes C_2-C_8 alkylene and R^9 denotes a nitrogen-containing heterocyclic aromatic residue or an amino group represented by the general formula



(R^{10} denotes hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkanoyl and R^{11} denotes hydrogen or C_1-C_4 alkyl or R^{10} in combination with R^{11} denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms), and

at least one pharmceutically acceptable inert carrier or diluent.

9. A pharmaceutical composition according to Claim 8 wherein the disease is inflammation, circulatory disease, gastrointestinal ulceration or allergic disease.

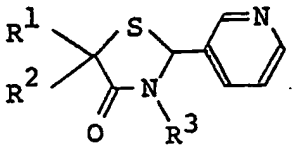
10. A pharmaceutical composition according to Claim 9 wherein the circulatory disease is DIC (disseminated intravascular coagulation) or endotoxin shock.

11. A pharmaceutical composition according to Claim 9 wherein allergic disease is asthma.

12. A pharmaceutical composition according to Claim 9 wherein gastrointestinal ulceration is gastric ulcer.

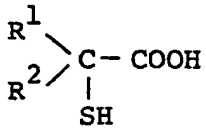
13. A pharmaceutical composition according to Claim 9 wherein inflammation is nephritis or rheumatism.

14. A method for treatment of the disease caus d by the platelet activating fact r, which comprises administering to a patient a pharmaceutically effective amount f at l ast one comp und represented by the general formula



wherein, R^1, R^2 and R^3 are as defined in Claim 8, or a pharmaceutically acceptable salt thereof.

15. A method of preparation which comprises reacting in an inert solvent a compound represented by the general formula



(II),

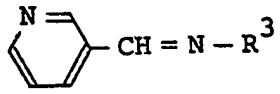
wherein R^1 and R^2 are the same or different and denote each

(i) a residue represented by the general formula

-A-R^4

wherein, A denotes a single bond, C_1-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene and R^4 denotes hydrogen, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl, or C_1-C_8 haloalkyl,

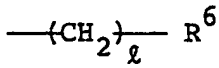
with a compound represented by the general formula



(III)

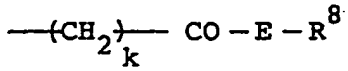
wherein R^3 denotes hydrogen, C_1-C_2 alkyl, allyl, 2-propynyl, or a residue represented by

(a) the general formula



wherein, R^6 denotes halogen, an aryl substituted or unsubstituted by one or more hydroxy or C_1-C_4 alkoxy groups, or a residue represented by the general formula -D-R^7 (D denotes oxygen or sulfur and R^7 denotes hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkanoyl) and ℓ denotes an integer of 2 to 4,

(b) the general formula

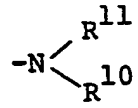


wherein, E denotes oxygen, sulfur, imino, or C_1-C_4 alkylimino, R^8 denotes hydrogen or C_1-C_4 alkyl, or -(E-R^8) denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms, and k denotes an integer of 1 to 3, or

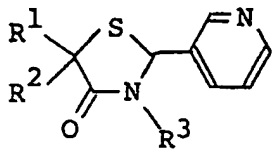
(c) the general formula

-F-R^9

wherein, F denotes C_2-C_6 alkylene and R^9 denotes a nitrogen-containing heterocyclic aromatic residue or an amino group represented by the general formula



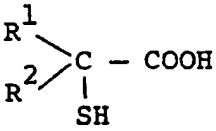
(R^{10} denotes hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkanoyl and R^{11} denotes hydrogen or C_1-C_4 alkyl or R^{10} in combination with R^{11} denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms), to obtain a 2-pyridylthiazolidin-4-one derivative represented by the general formula (I)



(I),

wherein R^1, R^2 and R^3 are as defined above.

16. A method of preparation which comprises reacting in an inert solvent a compound represented by the general formula (II)



(II),

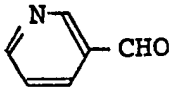
wherein R^1 and R^2 are the same or different and denote each

(i) a residue represented by the general formula

-A-R^4

wherein, A denotes a single bond, C_1-C_8 alkylene, C_2-C_8 alkenylene, or C_2-C_8 alkynylene and R^4 denotes hydrogen, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl, or C_1-C_8 haloalkyl, or

with a compound represented by the formula



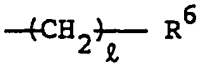
(IV)

and with a compound represented by the general formula

H_2N - R^3 (V)

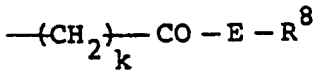
wherein R^3 denotes hydrogen, C_1-C_2 alkyl, allyl, 2-propynyl, or a residue represented by

(a) the general formula



wherein, R^6 denotes halogen, an aryl group substituted or unsubstituted by one or more hydroxy or C_1-C_4 alkoxy groups, or a residue represented by the general formula -D-R^7 (D denotes oxygen or sulfur and R^7 denotes hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkanoyl) and ℓ denotes an integer of 2 to 4,

(b) the general formula

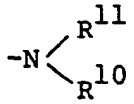


wherein, E denotes oxygen, sulfur, imino, or C_1-C_4 alkylimino, R^8 denotes hydrogen or C_1-C_4 alkyl, or -(E-R^8) denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms, and k denotes an integer of 1 to 3, or

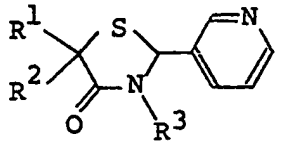
(c) the general formula

-F-R^9

wherein, F denotes C_2-C_6 alkylene and R^9 denotes a nitrogen-containing heterocyclic aromatic residue or an amino group represented by the general formula



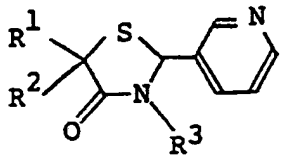
(R^{10} denotes hydrogen, C_1-C_4 alkyl, or C_1-C_4 alkanoyl and R^{11} denotes hydrogen or C_1-C_4 alkyl or R^{10} in combination with R^{11} denotes a 5- to 7-membered cyclic amino group which optionally contains other hetero atoms), to obtain a 2-pyridylthiazolidin-4-one derivative represented by the general formula (I)



(I),

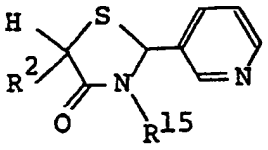
wherein R^1, R^2 and R^3 are as defined above.

17. Use of a compound represented by the general formula



wherein R^1, R^2 and R^3 are as defined in Claim 8, and/or its pharmaceutically acceptable acid addition salt for the manufacture of an anti platelet activating factor drug.

18. A method of preparation which comprises reacting in an inert solvent a compound represented by the general formula



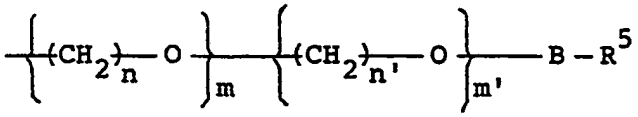
wherein R^2 denotes each

(i) a residue represented by the general formula

-A-R^4

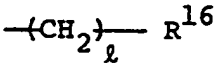
wherein, A denotes a single bond, C_1-C_8 alkylene, C_2-C_8 alkexylene, or C_2-C_8 alkynylene and R^4 denotes hydrogen, C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl, or C_1-C_6 haloalkyl, or

(ii) a residue represented by the general formula



wherein, B denotes a single bond or C_1-C_6 alkylene, R^5 denotes hydrogen, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_3-C_8 cycloalkyl, substituted silyl or substituted or unsubstituted aryl, n and n' denote each an integer of 2 to 4, m denotes an integer of 1 to 3, and m' denotes an integer of 0 to 2,

R^{15} denotes C_1-C_6 alkyl, allyl, 2-propynyl, or a residue by (i) the general formula

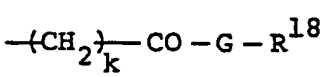


(wherein, R^{16} denotes an aryl group substituted or unsubstituted by one or more C_1-C_4 alkoxy groups, or a residue represented by the general formula

-D-R^{17}

wherein R^{17} denotes C_1-C_4 alkyl and D denotes oxygen or sulfur, and ℓ denotes an integer of 2 to 4.),

(ii) the general formula



wherein, G denotes oxygen atom or C_1-C_4 alkyliimino, R^{18} denotes C_1-C_4 alkyl, or the G-R^{18} combination denotes a 5- to 7-membered heterocyclic amino group which may or may not contain other hetero atoms, and k den tes an integer of 1 to 3, r

(iii) the general formula

-F-R^9

wherein F and R^9 are as defined in Claim 15,

with a c mpound represented by th g neral formula

R^{14}-X

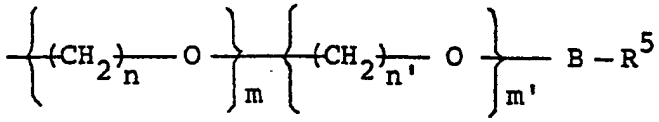
wherein X denotes a leaving group and R^{14} denotes each

a) a residue represented by the general formula

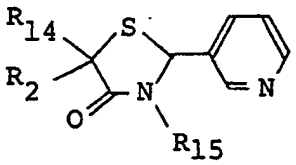
-A-R^4

wherein A and R^4 are as defined above, or

b) a residue represented by the general formula

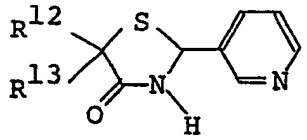


wherein, B, R^5, n, n', m, and m' are as defined above, to obtain a 2-pyridylthiazolidin-4-one derivative represented by the general formula



wherein R_2, R_{14} and R_{15} are as defined above.

19. A method of preparation which comprise reacting in an inert solvent a compound represented by the general formula



wherein R^{12} and R^{13} are the same or different and denote each a residue represented by the general formula

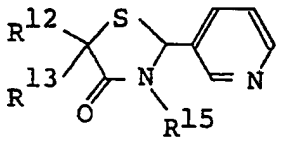
-A-R^4

wherein A and R^4 are as defined in Claim 15,

with a compound represented by the general formula

R^{15}-X

wherein R^{15} and X are as defined in Claim 18, to obtain a 2-pyridylthiazolidin-4-one derivative represented by the general formula



wherein R^{12}, R^{13} and R^{15} are as defined above.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number EP 88 30 4583

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,A	EP-A-0 004 129(IMPERIAL CHEM. IND.) * Claims 1-5 * --	1-7,15	C 07 D 417/04 A 61 K 31/44
A	EP-A-0 010 420 (ELI LILLY) * Claims 1,2 * --	1-7	
D,A	CHEMICAL ABSTRACTS, vol. 97, no. 25, December 20, 1982, page 853, abstract no. 216166j Columbus, Ohio, US & JP-A-82 85380 (HISAMITSU PHARM. CO. INC.) 28-05-1982 * Abstract * --	1,8	
P,A	EP-A-0 256 687 (SUMITOMO) * Claims * -------	1-13, 15-19	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 D 417/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-13, 15-19

Claims searched incompletely:

Claims not searched: 14

Reason for the limitation of the search:

Method for treatment of the human or animal body by surgery or therapy (See art. 52(4) of the European Patent Convention)

Place of search	Date of completion of the search	Examiner
The Hague	11-08-1988	HENRY

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document